# HANDBOOK OF TROPICAL DERMATOLOGY AND MEDICAL MYCOLOGY

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# TROPICAL DERMATOLOGY

## AND MEDICAL MYCOLOGY

edited by

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Amsterdam

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## DISEASES DUE TO ALLERGY, MALNUTRITION, AND METABOLIC DISTURBANCES



## TUMOURS

# CHAPTER 34

# THE DERMATOZOONOSES

## (Introduction)

R. D. G. PH SIMONS

Amsterdam

Independently of any entomological subdivision of arthropods, vermes etc., dermatology differentiates the following arthropodal zoonoses

A *Endodermatozoonoses* those parasitic infestations in which the parasite burrows deeply into the skin and remains embedded, as is the case of certain acari, and the larvae of some oestridae, etc.

B *Epidermatozoonoses* those skin diseases in which the parasite attaches itself to but does not burrow into the skin, as is the case of other acari (ticks) and lice. (DARIER called these affections "epizoonoses" )

C. *Transient-dermatozoonoses* or *transito-zoonoses* those in which the parasite attacks the skin, without attaching itself to it, as is the case of hemiptera (bugs), some diptera (e.g mosquitoes) pulicidae (fleas) lepidoptera (moths) etc. By the time the larvae of some of these parasites burrow into the skin, the former should be classified in group A.

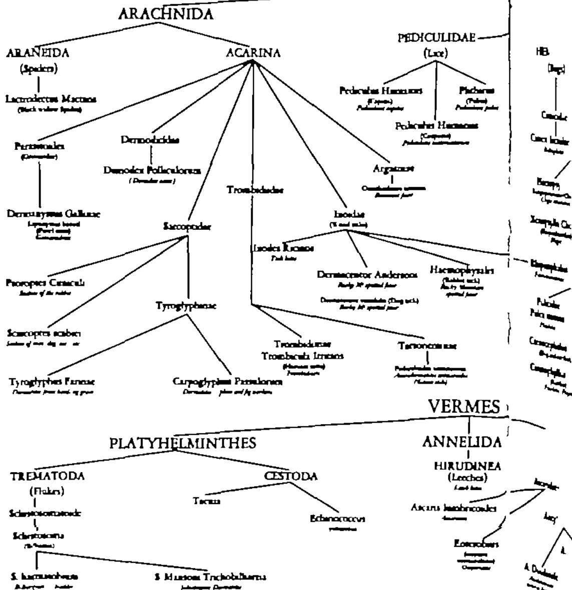
Animal parasites of man may with their hairy legs, transmit disease germs while other vectors or transmitters are the necessary intermediate hosts wherein the morbific agent may or may not, spend a part of its lifecycle. Yet another group of parasites, viz especially those belonging to group A and partially C, do not transmit disease germs but are themselves responsible for the patient's complaints, either mechanically or by the production of toxic substances or antigens that cause mainly pruritus and urticaria, and possibly also, certain so called id reactions" Barring exceptions, it almost looks as if there exists a kind of "division of labour" among the several groups viz A. Endodermatozoonoses—no infectious diseases and no allergic reactions (?) B Epidermozoonoses—sometimes infectious diseases e.g the rickettsial diseases and C. Transito-zoonoses local or general allergic reactions, and sometimes infectious diseases.

Apart from the dermatozoonoses other animal parasitogenic affections which are of importance dermatologically will be described in this section

# DISEASES DUE TO ANIMAL ORGANISMS (EXCL

TABLE OF ORIEN TATION (EXC

ARTHROPODA



## S (EXCLUDING PROTOZOA)

**TATION (SIMPLIFIED)**

INSECTA

HEMIPTERA (Bugs)
Cimicidae
Cimex lectularius

SIPHONAPTERA (Fleas)
Hectopsyllidae
Xenopsylla Cheopis
Rhopalopsyllus
Pulicidae
Pulex irritans
Ctenocephalus canis
Ceratophyllus fasciatus

DIPTERA (Flies)
Orthorrhapha
Nematocera
Culicidae
Brachycera
Tabanidae
Cyclorrapha
Aschiza
Schizophora
Muscidae
Glossina
Wohlfahrtia
Sarcophaga
Calliphora
Cordylobia Anthropophaga
Oestridae
Cuterebrinae
Dermatobia Hominis
Oestrinae
Gastrophilus
Haemorrhoidalis
Hypoderma

LEPIDOPTERA (Moths)
Euproctis Chrysorrhoea
Hemerocampa Leucostigma
Automeris Io

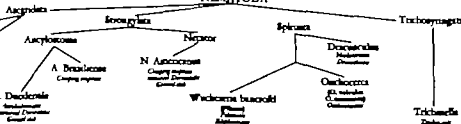



Fig 588 Relating to chapter 35 by M. E. OBERMAYER and J W WILSON

# DISORDERS CAUSED BY ANIMAL ORGANISMS[1]

MAXIMILIAN E. OBERMAYER – Los Angeles
J. WALTER WILSON – Los Angeles

This title, "Disorders Caused by Animal Organisms," was carefully chosen as the one most likely to include all of those dermatologic deviations from normality which are incurred by human beings as the result of contact with other members of the animal kingdom. Not all of these changes deserve the term "disease"; some are merely injuries such as bites, scratches or stings; some are irritations, such as resulting from the hairs of certain caterpillars; some are represented simply by pruritus due to the sensations produced by the organisms crawling about the body.

It is also not appropriate to limit this study by entitling it "Parasitology," since many conditions of dermatologic interest result from the activities of organisms which do not satisfy the necessary criteria for classification as parasites, that of living within or on the surface of the human body and obtaining nourishment in some manner through such a relationship.

Many books have limited the discussion on this subject to entities of importance in certain geographic areas alone. The present volume intends to furnish more complete information such as may guide the physician in other portions of the globe as well.

It is also evident that there can be no sharp limitation by virtue of the zoological classification of the offenders, since among the organisms which trouble human beings on occasion are included representatives of every Phylum of the animal kingdom. Although the majority belong to the Phylum "*Arthropoda*" and a large proportion of the remainder to the Phylum "*Helminthes*" or "*Vermes*," we must consider in addition several *Protozoa* and occasional members of other Phyla.

[1] We are indebted to Dr. Edward J. Bowen, Jr. for the compilation of the literature.

exemplified by harmful jelly-fishes (*Coelenterata*), sponges (*Porifera*) and sea urchins (*Echinodermata*). There are even examples among the *Chordata* such as poisonous snakes, reptiles, fishes and mammals.

It is not even true that the reaction between the invading organism and the host is always detrimental to the latter For example the malarial parasite has been of service in the treatment of some forms of syphilis and the venom of the bee has been utilized in ameliorating arthritis. Usually however it is the fact that deleterious pathologic effects are produced in the afflicted person which makes it necessary to study an animal organism in this regard.

The list of diseases which are transmitted to man in the course of attacks by animal organisms is long and varied, and includes many serious and important entities which will be discussed later in the appropriate chapters. In brief, *mosquitoes* carry malaria, dengue fever yellow fever filariasis and encephalomyelitis. *Lice* transmit epidemic typhus and relapsing fever *fleas* transmit tularaemia, bubonic plague, endemic typhus and leptospirosis. *Ticks* transfer Rocky Mountain spotted fever as well as other spotted fevers known as the Eastern, Neotropical and Oriental varieties. Ticks also transmit tularaemia, Q fever and encephalomyelitis. *Flies* carry the organisms of a host of diseases including typhoid fever, cholera, yaws, bejel, pinta, trachoma, anthrax, onchocerciasis, oroya fever, kala-azar and espundia. There are many examples in which an animal organism serves not only to transmit a disease but also as reservoir in maintaining and propagating its causative organisms by acting as an intermediate obligatory host, for example as in malaria.

Medical science has attempted to intervene to protect human beings from the objectionable activities of animal organisms at all conceivable points. Lethal or paralytic chemicals are used in the natural habitats of parasites, in the environment surrounding the prospective hosts and at times on the bodies of the hosts themsel es, even after invasion occurs. Substances known to repel parasites are useful even though they are not parasiticidal. Screens nets, protecti e clothing and other mechanical means of protection are utilized sometimes these may be advantageously impregnated with repellents or parasiticides of long lasting nature. Much progress has been made in recent years in such chemical methods the subject is reviewed completely by GOLDMAN and his associates. In addition, various medicinal, mechanical and, at times, immunologic methods are employed after the host has been invaded to combat the specific pathologic effects sustained. In this work the biologist has been of inestimable help to the physician by studying each parasite to discover its peculiar susceptibilities

It is noteworthy that many parasitic infestations are characterized by the gradual development of a so-called "immunity" by most of those individuals frequently exposed this "immunity" actually "*desensitization*" does not usually furnish freedom from subsequent bites, but simply renders them less and less annoying even to the point of imperceptibility Thus, natives frequently believe that parasites indigenous to the region do not bite them nevertheless, diseases transferred by such bites may be observed to be contracted even in the absence of symptoms referable to the biting The antibodies produced in the

course of some of these processes have lent themselves to certain diagnostic procedures such as intra-cutaneous testing and precipitation and complement fixation reactions (BAER and YANOWITZ)

Attempts to produce antigens by which susceptible individuals may be immunized against the bite of a specific parasite have been only partially successful perhaps largely because the antigens do not consist in sufficiently great proportion of the salivary secretion of the insect. It has even been facetiously suggested that fleas might be trained to spit into containers and thereby yield a more representative antigen. It is even less likely that artificial immunological methods can be developed which will confer resistance against insects in general, since all reactions of this nature hitherto examined seem to be narrowly specific.

A schematic classification of animal organisms known to cause disorders of importance to dermatology is reproduced on pages 852 and 853 in the form of a chart (Fig 588)

It is admittedly incomplete being principally limited to those organisms of practical importance in the United States of America. In order to keep the chart readable, no attempt was made to include data on the zoological classification of the organisms referred to such details when important will be contained in the appropriate sections of the text to follow

There is ample evidence indicating that the living organisms which are man's enemies were in existence long before him and will long outlast him. Processes of mutation allow them to develop resistance against each new weapon he discovers. Unceasing vigilance and research are the only methods by which he may survive DWIGHT PIERCE of the Los Angeles County Museum presented as an interesting example of such persistence the fact that at least ten species of beetles have been continuously present in Southern California for a million years, being found in all strata of the La Brea tar pits which date from earliest Pleistocene times Some species (notably Eleodes acuticaudata La Conte) have made no observable changes in form or structure by virtue of evolution in all those eons of time

## ARACHNIDA

### SARCOPTIC MITES

The most important and by far the most common human infestation caused by an organism of this group is the common form of scabies which is the subject of a later special chapter (36) We were given the task of discussing a number of entities which result when human beings come into close contact with various animals infested with mites similar to those causing human

scabies. Among the domesticated group swine sheep cattle, horses mules camels goats dogs and cats are subject to infestation by organisms more or less closely allied to the human *Sarcoptes* each animal species being favoured by its own variety of mite In like manner wolves lions tigers and foxes have their special infestations. An extensive listing of many genera and type of species of mites known to infest mammals birds and reptiles has been reported by RADFORD.

In general all of these parasites affect man less severely than does his own species of *Sarcoptes* causing usually only moderate pruritus and a diffuse polymorphous eruption in which the burrows so characteristic of human scabies are as a rule entirely absent. In most instances these infestations are easily cured since the mites are not imbedded into the skin. Simple change of clothing and frequent bathing usually suffice after the offending animal host is removed or cured. Special features of some of the most common of these forms of animal scabies are as follows

*Scabies of the horse* occurs in stable workers especially grooms After a short incubation period, sometimes but a day bright red conical follicular papules appear capped by a haemorrhagic crust. The flexor surfaces of the arms and the chest and abdomen are the favoured sites the genitalia are usually spared. When these lesions are excoriated urticarial wheals frequently ensue. It is seldom necessary to use scabeticides to effect a cure frequent bathing and clean clothing usually suffice especially if the animal hosts are treated and more care is taken to avoid close contact.

*Scabies of the cat* is caused by a small mite not correctly classed as a sar coptes. In man, the lesions are usually small papules topped by minute vesicles. Removal of the animal or its successful treatment for its infestation usually results in cure of the human disorder as well.

*Scabies of the dog* produces in human beings erythematous macules and papules occasionally topped by vesicles. The areas most frequently involved are those contacted by the animal, such as cheeks ears, neck and arms. The method of treatment is the same as that for the previously discussed infesta tions.

*Scabies of the birds* Minute red mites (most commonly a blood sucking variety known as *Dermanyssus gallinae*) which commonly infest birds, fowls bats mice and guinea pigs, are capable of producing eruptions on the skin of man, usually involving the covered portions of the body such as the flexors of the extremities the axillae, breasts abdomen and buttocks. Small, bright red papules appear which as a rule are thoroughly excoriated almost immediately and are frequently accompanied by urticarial wheals. The principal difficulty in diagnosis lies in the failure to think of the possibility of an infestation the history of the presence of such pets should suggest a careful search for mites. Treatment consists of freeing the environment of the sour ces of the infestation followed by the application of mild antipruritic lotions to the lesions.

## RAT MITES

SHELMIRE and DOVE reported in 1931 their observations on a large number of cases of human infestation with a species of blood sucking mites (*Liponyssus bacoti* Hirst) which normally parasitizes rats. In many instances they found that the organisms had been acquired in motion picture theaters and other public buildings. In adults the ankles are principally involved but bites also occur on the face, neck, shoulders and belt line, especially in children. The lesions are papules or wheals frequently exhibiting central puncta and vesicles and showing the same tendency toward grouping observed in flea bites. When the diagnosis is in doubt and mites are suspected but not discoverable, fly paper spread upon the floors may reveal their presence.

Especially important is the fact that these mites transmit the specific *Rickettsia* of endemic typhus (Brill's disease). The dermatosis itself requires no treatment beyond the usual antipruritic lotions or pastes containing phenol or menthol. To prevent reinfestation and the spread of typhus, however, it is necessary to exterminate the rat hosts and fumigate the buildings to destroy the mites.



589. Poultry mite or dermanyssus gallinae



590. Rat mite or liponyssus bacoti

## FOOD MITES

Several varieties of mites closely related to acari are found in great numbers on certain foods, especially when contaminated additionally by molds or insects. Grocers, food packers, and transportation workers acquire a dermatitis limited usually to the parts of the body which are brought into contact with these materials, such as the hands, forearms and the anterior surface of the trunk. The eruption usually consists of small pointed erythematous papules sometimes topped with vesicles or pustules; pruritus is intense

Each variety of food stuff is usually parasitized by a particular species of mite. Cheese, straw and grain foods may contain *Tyroglyphus farinae*; copra frequently contains *Tyroglyphus longior*; onions, especially when decaying, may be infected with *Rhizoglyphus hyacinthi*; and tobacco, prunes, dates and figs may harbour *Carpoglyphus passularum*. The famous LINNAEUS knew of the significance of such mites, for he correctly attributed the dermatitis occurring in children who were dusted with powdered meal to the mites which it contained. Workers who handle linseed before it is compressed for the oil are subject to a similar dermatitis.

The more susceptible and severely involved individuals may need to change their occupation entirely. Tyroglyphidae may be killed by exposure to dry heat at 150° F. Protective clothing and various repellents may be tried. β-Naphthol in 5 per cent. ointment is advised for *copra itch*. Avoidance of reinfestation results in cure.

#### PEDICULOIDES (GRAIN ITCH MITE)

A small, grayish-yellow mite, visible to the naked eye, and called *Pediculoides ventricosus* parasitizes the larvae, caterpillars and chrysalis of various insects which infest grain and straw. Persons contacting these materials, such as harvesters or those sleeping on straw or straw mattresses, acquire a dermatitis which varies considerably in severity according to the number of organisms involved and the sensitivity of the individual. In mild cases only those portions of the body in actual contact with the offending substance are involved; in severe cases the entire trunk, neck and face are covered. The resulting eruption consists of bright red papules 2 to 4 mm in diameter, often capped by a vesicle or pustule; the larger lesions are somewhat urticarial and frequently haemorrhagic in appearance, only to pale out on examination under diascopic pressure. Constitutional symptoms may occur, such as mild fever and albuminuria. The disorder is called by various names: scientifically, *acarodermatitis urticarioides* (SCHAMBERG) and colloquially, *grain itch*, *barley itch*, *straw itch*, *prairie itch* and *swamp itch*.

The eruption may be confused with varicella especially when accompanied by a constitutional reaction. The lesions lack the umbilication of varicella, however, and the fact that it is usually adults who are infested is helpful.

Treatment consists of the use of antipruritic paste or lotion and the avoidance of further contact. An epidemic of this infestation which occurred in Italy in handlers of beans infested with weevils was controlled by the use of DDT according to SOLETA.

#### DEMODEX FOLLICULORUM

A worm-shaped mite of microscopic size, *Demodex folliculorum*, occurs almost ubiquitously in the follicular openings, especially in seborrheic individuals. The infestation is more abundant on the face, especially the forehead,

nose and chin, less frequently it is encountered in the follicles of the eye lashes and meibomian glands and on the trunk. The extremities are usually not involved. According to AYRES this organism is at least partially responsible for rosacea in some cases especially in women who cleanse the



591 – 592. Demodex folliculorum in the sebaceous gland.
*(Beek – The Hague)*

skin with cream alone he described a resultant follicular hyperkeratosis termed "pityriasis folliculorum" which caused the skin to feel like a "*nutmeg grater*". Cats and dogs may be infested with similar organisms which produce in them a severe disease occasionally transmitted to man. The resulting pustules contain large numbers of demodices.

Cure is easily obtained by using mild scabeticides such as 5 per cent. sulfur or ammoniated mercury ointment.

CHIGGERS (HARVEST MITES)

Mites are the larger arachnida, frequently incorrectly considered to be insects. Several organism belonging to a family called [illegible]idudae and collo-

curious manner assisted by the secretion by the organism of a salivary substance which dries into a tubular structure called a "histosiphon" extending through the skin of the host. (See Fig 144 Vol. I.)

The cutaneous reaction to the bite is an erythematous macule which becomes a papule in a few hours surrounded by an erythematous halo at times haemorrhagic. In some lesions the red mites may still be seen in the centre in others simple haemorrhagic puncta are visible. The pruritus develops some time after the bite and is intense, especially after the body has become warm in bed. Many of the papules become nodular and some persist for weeks continuing to itch severely The resulting extreme excoriation and secondary infection causes the disorder to be resistant to therapy Occasionally sensitization of the skin occurs and eczematous "id" lesions ensue requiring weeks or months for healing

The sudden appearance of severely pruritic "bites" in a person who has walked through or otherwise contacted grass suggests the diagnosis. Inspection of the lesions with a lens may reveal the organisms. The application to the "bites" of 12 per cent. benzocaine in flexible collodion is gratifying Dusting the clothing with sulfur is of benefit in prevention and even its oral administration has been advised. It is essential to recognize the presence of secondary pyogenic infection early and begin appropriate treatment. If exposure is anticipated, impervious clothing is efficiently protective its impregnation with parasiticides has also been suggested. Repellent chemicals such as RUTGERS 612 may also be employed.

## TICKS

Several varieties of ticks (*Ixodes*) attack human beings on occasion although as a rule they favor various other animal hosts when available. Ticks are found in many wooded regions both on vegetation (hence the common term "*wood tick*") and on animal hosts. Many species have a complicated life cycle preferring different hosts in the larval and adult stages Some may live as long as three years.

Ticks are large (4 to 5 mm) rounded acarines with the usual 4 pairs of legs brown or yellow with spots in some varieties and possessing a hard body covering The head is attached to the body in a fragile manner so that when it is deeply imbedded in the skin in the process of biting any attempt at forcible removal of the tick beheads it, leaving the barbed mandibles in the wound as an infective foreign body After attachment the organism engorges itself with blood, enlarging to the size of a large pea and frequently remaining in situ for days. It is at this stage when it is most frequently discovered by the patient and unless he has encountered ticks before, the true nature of the disorder is seldom realized the appearance suggests a newly formed "tumour" perhaps recognized as containing bluish blood. Only in hypersensitive individuals is an erythematous reaction observed around the "bite" occasionally accompanied by lymphadenopathy

It is best to attempt to cause the tick to release its hold by bathing it in some toxic, volatile oil such as gasoline or turpentine rather than attempt removal by force leaving the mandibles imbedded to serve as a further irritant and source of infection is thus avoided. If parts of the head are broken



593 Wood tick with head imbedded in skin There is little inflammatory reaction

off in the wound it is necessary to remove them completely by a miniature surgical excision to avoid the transmission of disease or tick paralysis which may follow (see below).

Tick "bites" sometimes result in dermal nodules varying from 0 6 to 2.5 cm in diameter which may persist for months. When the history of the "bite" is not obtained such nodules are difficult to diagnose. WINER and STRAKOSCH have pointed out that the histopathologic findings may suggest lymphoblastoma in the early phases and subepidermal fibrosis after the nodules have persisted for several months

Ticks serve as vectors for several infectious diseases *Dermacentor andersoni* carries the organism of Rocky Mountain spotted fever *D variabilis* and *occidentalis* frequently transmit tularaemia. African relapsing fever is inoculated by several varieties as are the *Mediterranean exanthematous fever* *terrapa peruana plague yellow fever* and *Sao Paulo typhus* It is not even necessary that an actual "bite" be sustained to transfer these diseases contamination of a scratch or wound with a crushed tick or its excreta may suffice (BYFIELD *et al*)

A toxic muscular paralysis known as *tick paralysis* occasionally occurs

following "bites" of several species especially in infants and young children. Complete removal of the insect is mandatory and results in recovery failure to remove it may be fatal. So-called *Ixodism* manifested by vomiting, urticaria and generalized toxic manifestations has been described.



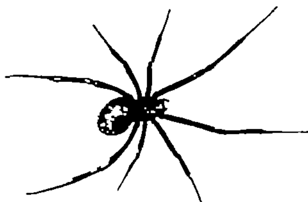
594 Dermacentor andersoni.
(*cf* *Vol I Fig 522*)

**SPIDERS**

Spiders are equipped with fangs and poison glands by which they immobilize or kill their prey Only the larger spiders are able to penetrate the human skin Many of the poisonous species of the world belong to the genus Latrodectus of which the species *L. mactans* (Fig 595) will serve as an example. This is the "black widow" spider of the United States of America (so called because the female kills its mate), whose venom by dry weight is 15 times as potent as that of the rattlesnake. It is a large shiny black spider with long slender legs on its ventral surface there is a red or yellow spot shaped like an hourglass. Its "bite" may be serious and has caused a few deaths especially in small children. In adults it is frequently the cause of severe constitutional symptoms especially if multiple bites are sustained and particularly if the genitalia are involved Any part of the body may be "bitten" but the genitalia or buttocks are frequently attacked while the person is sitting in an outdoor privy The bite causes intense local pain, regional oedema spastic cramps of the extremities rigidity of the abdomen with nausea and vomiting, headache ringing in the ears, dizziness generalized pain and a state of anxiety The blood pressure rises as much as 30–40

mm later shock and delirium may occur Generalized toxic erythemas are not uncommon.

Treatment should be quickly begun and according to FRAWLEY and GINSBERG should be administered as follows bedrest, soap-solution enema, forcing of fluids 20 ml of a 10 per cent. solution of magnesium sulfate intravenously to combat hypertension and muscle spasticity morphine hypodermically for relief of pain and peroral sedation. Calcium gluconate should be given in one-gram doses intravenously and repeated at hourly intervals according to HALTER and KUGEL. An antiserum produced by animal inoculation has been recommended as well as human convalescent serum. Locally



595 Latrodectus mactans o black widow spider

the "bite" should be treated with tincture of iodine followed by wet dressings of potassium permanganate

Close observation may reveal the presence of these organisms in the environment and naphthalene (2 oz. to each cubic foot of space) and kerosene with the addition of 1 to 10 per cent. amyl alcohol has been recommended to eliminate them. Other insecticides seem to be of lesser value

In South Africa *L. concinnus* and *L. indistinctus* are the prevaling species in Australia *L. hasselti* and in Russia *L. lugubris* are known to be toxic. Members of other genera are venomous such as *Chiracanthium* in Europe and *Glyptocranium* in Peru.

Neurotoxicity giving rise to bradycardia salivation, lacrimation paralysis and even death have resulted from the bites of certain tropical *Scorpions* (RILEY and JOHANNSEN) *Centruroides suffusus* found in the Southern United States and Mexico is one dangerous variety

## INSECTA

The Insects which parasitize man are of great importance especially in time of war because they act as vectors for the spread of several epidemic diseases. In addition, the lowering of morale and the distraction from important duties induced by the intense pruritus resulting from some infestations is well recognized.

Insects are easily differentiated from mites (*Arachnida*) by the presence of three pairs of legs instead of four they are commonly referred to as "hexapods" Most of those of medical importance are zoologically included in six orders *Anoplura*



596 Nits attached to the hairs in pediculosis capitis.

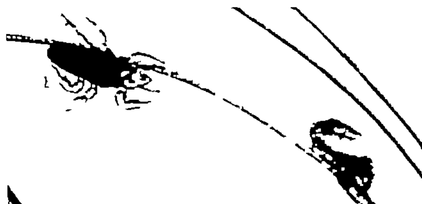
are bloodsucking lice *Hemiptera* are bedbugs *Siphonaptera* include fleas *Diptera* are two-winged flying insects, including mosquitoes and flies *Hymenoptera* include bees, ants, wasps and hornets and *Lepidoptera* apply to moths and butterflies.

An insect bite usually consists of a macule which in susceptible individuals, often soon becomes a papule or wheal A small central haemorrhagic punctum frequently makes differentiation from urticaria easy There is a distinct tendency toward close grouping of the lesions in an asymmetric fashion difficult to reconcile with non-parasitic diseases. Insect bites must however be considered in the differentiation of all pruritic papular and urticarial eruptions wherever the diagnosis is not otherwise obvious.

### PEDICULI (LICE)

Human infestation with lice occurs in three varieties, known as *pediculosis*

*capitis p corporis* or *vestimentorum* and *p pubis* Since animals do not harbour them direct contact with infested persons or their clothing is usually the mode of transmission. Lice are sometimes air-borne on the wind and con tact with various other fomites such as upholstered seats and chair-backs is sometimes responsible for the infestation. Each of the three forms is caused by a different species of pediculus although the head louse is considered by some observers as a variety of the species causing pediculosis corporis. The three species are easily differentiated by their shape it is almost as accurate however to decide which is present by observing the portions of the body which are selected for invasion.



597 Head louse and nit
*(Orig G C sta – Belo Horizonte)*

*Pediculus Capitis*

The head louse, perhaps better termed the "scalp-l use" is a grayish br wn narr w insect from 2 t 4 mm long the female is larger than the male This infestati n occurs most frequently n the scalp f women and girl ince l ng hair supports it better than short. The favoured locations are the nape and the temp ral areas but the entire scalp may bec me heavily infested The insects themselves frequently elude the examiner by crawling rapidly away and the diagnosis is usually made by bserving the eggs (nits) These are attached t the hair hafts by a gelatinous ubstance which hardens int chitin. Their val shape specific ize firmness and the tenacity with which they adhere t the hair serve t di tingui h them fr m dandruff when in doubt micros opic examinati n is c nclusive

The diagnosi hould be u pected whenever exc riations are bserved in the nape and auricula areas sec ndary py derma r impetiginous infec tion in these regi n i highly suggestive In severely neglected cases the

hair becomes matted together by dried purulent exudate and a foul odour is produced. Regional lymphadenopathy is common.

Treatment may be effectively carried out by using any of a large number of parasiticides. The popularity of the old treatment with equal parts of kerosene and olive oil declined some years ago in favour of a hydrocarbon-oil containing copper oleate (Cuprex(R)), said to kill the ova as well as the lice. Benzyl benzoate in the 25 per cent. emulsion is effective. For delousing on a large scale DAVIS recommended 20 per cent. solution of phenyl cellosolve in equal parts of isopropyl alcohol and water. A 3 to 5 per cent. solution of DDT has also been recommended by SCOTT. Whichever of these preparations is selected it is then thoroughly applied to the scalp which should be tightly wrapped with an impervious material; the medicament is allowed to act for at least 6 hours, followed by thor-



598. Pediculosis corporis: nit in fibres of clothing

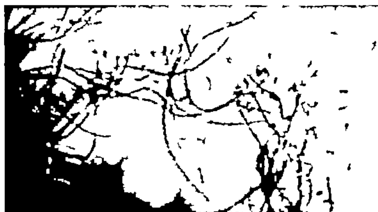
ough shampooing. The hazard of fire must be avoided when kerosene is used. It has been proved that vinegar does not detach the nits as formerly believed. Subsequently it is usually necessary to begin thorough treatment for the impetiginous pyoderma which is so frequently also present. If cure is in doubt, the parasiticide should be reapplied in ten days.

*Pediculus Corporis (Vestimentorum)*

These organisms inhabit the seams of the clothing where they deposit their eggs and go through their life cycle, approaching the human body only to feed by sucking blood. Except in heavily infested hairy persons they are seldom to be found on the skin and the diagnosis must be made by inspection of the seams of the clothing. The parasite is larger than the head-louse and is of a lighter colour; otherwise there is such a close resemblance that some zoologists believe them to be simply variants of a single species. The

eggs may remain viable in unworn clothing for three weeks, hatching when it is again worn. They are attached to the fibres by a continuous secretion

Individual susceptibility varies from person to person this has been attributed to variations in body odour owing to differences in apocrine gland secretion. The typical macule or papule with the central punctum which is produced by the bite is seldom seen intact because the intense pruritus soon causes extensive linear excoriations in the production of which considerable anger is a prominent feature. The favoured sites are the shoulders trunk and buttocks where there is more intimate contact with the clothing In persons infested over long periods considerable hyperpigmentation results presenting then the so-called *vagabond's skin* with eczematization, new excoriations secondary pyoderma and the scars of old linear scratches. Occa-



599 Pediculosis pubis of hairs around the nipple.

sionally a systemic reaction occurs in severe infestations accompanied by fever and headache

Body lice transmit the organisms responsible for typhus fever trench fever and recurrent febrile spirochaetosis these are contained in the faeces of the lice and may be inoculated into breaks in the skin by the excreta or by crushed organisms even in the absence of bites.

Treatment is primarily sterilization of the clothing and thorough bathing of the body In hairy individuals a search may reveal nits attached to hair shafts as in pediculosis capitis these should be removed. For the delousing of large numbers of people the spraying of 5 to 10 per cent. DDT in pyrophyllite powder beneath the clothing without its removal from the body has been recommended by AHNFELDT one application is said to be effective and to prevent reinfestation for from three to four weeks. Secondary pyogenic infection and eczematous sequelae must receive appropriate therapy

*Pediculus (Phthirius) Pubis*

The crab louse or pubic louse is wider than its length in contrast to the two previously described varieties. It is transmitted primarily through sexual contact, but occasionally by means of bedding, clothing or toilet seats. The favorite location for the infestation is of course, the pubic hair but when lice are found in the axillae eyebrows or eyelashes this species is usually responsible The organisms attempt to bury themselves in follicular orifices and being pale in colour and somewhat translucent, may be difficult to see in persons who bathe infrequently The ova or nits are firmly attached to the hair shafts as in pediculosis capitis and are carried away from the follicles by the growth of the hair the duration of the infestation may thus be estimated by observing these distances. Palpation of the pubic region may suggest the diagnosis since the nits feel like grains of sand

The infestation produces pruritus, but excoriation followed by secondary



600 Pediculus pubis and pediculus capitis or vestimentorum.

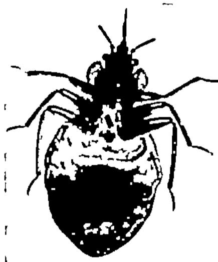
pyoderma is less common than in pediculosis corporis. Sometimes especially in light coloured skins pea to coin-sized grayish blue macular stains are observed (*maculae caeruleae*) which are said to be pathognomic of pediculosis pubis. This organism has not been convicted of transmitting disease.

Treatment may be carried out by the use of any of several parasiticides. Benzyl benzoate in 25 per cent. emulsion is effective. A solution of 3 to 10 per cent. DDT has been used successfully SHELANSKI and his associates recommended 5 per cent. isobornyl thiocyanate and 0.6 per cent. dioctyl sodium sulfosuccinate, worked into a lather and allowed to remain for ten minutes followed by bathing with soap and water two applications were employed. Cuprex(R) allowed to act for one hour after two applications and then bathed away is effective. There are many other worthy preparations. After any of these treatments the mechanical removal of

remaining nits followed by a period of close observation and retreatment in 10 days if necessary will prevent failures.

**BEDBUGS**

A single species, *Cimex lectularius*, is commonly found; other species of *Cimex* are recognized occasionally. It is a large insect ranging up to 6 mm in length with an oval, flattened body, a short broad head bearing prominent compound eyes and six long slender legs. The colour is reddish brown, becoming redder when the insect is engorged with blood. It lives in bedding and in crevices in the furniture, walls and floors of homes, hotels and public vehicles. It emerges usually at night only, to feed on its human host by



601 Cimex lectularius

sucking blood. Occasionally these insects have been found in the cages of experimental animals and in the nests of martins and bats.

The bite may or may not be felt by the host; it is followed in most instances by the development of a pruritic papule or wheal in which the central haemorrhagic punctum may be seen. The wheal may subside leaving a conical papule or nodule, or may enlarge and produce a vesicle or haemorrhagic bulla. The lesions are usually grouped together in pairs, threes or fours, since each insect obtains its nourishment from several different points in close proximity. The parts of the body usually involved are those easily accessible to the insect, especially the back, since the attack usually occurs in bed; ankles, wrists, buttocks and neck are also frequently involved. The

history may be helpful by revealing the fact that several new lesions are observed each morning *Cimex* bites tend to be purpuric which is an additional point of differentiation from urticaria.



602. Bedbug bites.

Treatment is primarily concerned with elimination of the insects from the environment Fumigation of the house with hydrocyanic acid or sulfur dioxide under the direction of experts is recommended The use of D.D T spray is said to be effective if thoroughly employed. Local applications to the lesions are seldom necessary antipruritic lotions or pastes may be prescribed. Bedbugs have been implicated in the transmission of the recurrent febrile spirochaetoses but their importance in this regard is dubious.

**FLEAS**

The commonest flea, *Pulex irritans* is distributed over most of the globe and lives in dwellings, refuse heaps and even in sand or earth. Several varieties or perhaps distinct species are important parasites on dogs cats, rats or squirrels, which hosts they seem to prefer only occasionally leaving them to attack man. They are reddish brown insects 2 to 3 mm in length with 6 long slender legs well adapted to prodigious leaps. They obtain nourishment by sucking blood from puncture wounds. Beyond the annoyance of their bites they are important vectors of several infectious diseases including plague, tularaemia, endemic typhus, and diseases caused by various bacteria, tropical protozoa and worms

Flea bites are usually grouped as described in the case of bedbugs and consist of pruritic papules or wheals with central haemorrhagic puncta. An

irritating salivary fluid which is injected at the time of the bite is apparently responsible for the urticarial wheal in addition, absorption of this toxin and its haematogenous spread may cause papular urticaria. There is great variation among individuals in the intensity of reaction to flea bites It is believed that all exposed persons are bitten indiscriminately but only those allergic to the injected saliva are aware of the attack. Certainly a sort of immunity develops in most individuals after repeated exposure during a period of a year In severe cases attempts to "immunize" persons by using an antigen prepared from fleas have given equivocal results perhaps because the antigen does not contain enough of the salivary toxin



603 Pulex irritans (Human female flea)

Treatment is of course primarily directed toward elimination of the organisms from the environment host animals should be treated refuse piles and other breeding spots cleared away and insecticides such as 5 per cent DDT in the aerosol bomb spray employed under rugs, in the crevices of furniture and about the bed. Repellents such as RUTGERS 612(R) (2 ethyl-1,3 hexanediol) seem to be efficient, and may be used on the bodies of affected persons. The local use of antipruritic paste or lotion on the bites will allay the itching

## CATERPILLARS

The larval caterpillars of certain moths (*Lepidoptera*) notably that known as the Brown-tail moth (*Euproctis chrysorrhea*) cause a dermatitis in sensitive persons Minute barbed spicules on the back and sides of the larvae seem to contain an allergen which induces in the area of contact erythematous macules occasionally progressing to urticarial and even vesicular reactions Such "hairs" may become lodged in the clothing and cause a generalized eruption even when such garments are subsequently worn again. Desensitization is claimed to be successful using an antigen prepared from crushed

larvae. The "puss caterpillar" (*Megalopyge opercularis*) also offends in a similar manner even more severely thousands of cases necessitating closure of schools have occurred in Texas on several occasions.

### OTHER INSECTS

Many additional insects too numerous to list here attack man on occasion and produce a wide variety of lesions and symptoms in addition to transmitting organisms of disease. Gnats mosquitoes, bees wasps and various types of flies, are included also certain beetles which exude a vesicant fluid on contact with the skin. The resulting lesions are macular papular haemorrhagic, urticarial vesicular or bullous as the case may be. In hypersensitive individuals local as well as systemic allergic reactions may occur at times sufficiently extensive to simulate angioneurotic oedema. Bee stings for example, have been followed by severe systemic manifestations even in the absence of pronounced local inflammation (HELM, OBERMAYER). It has not been clear whether the reaction is due to toxin from the bee (histamine, formic acid) or less likely to pollens implanted at the time of the sting The larva of the bot fly produces painful inflammatory nodules. Persons hyper sensitive to the *deer fly* may obtain relief by injections of an antigen prepared from macerated flies (MEASE)

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CHAPTER 36

# SCABIES

C. H. BEEK – The Hague
KENNETH MELLANBY – Ibadan (Nigeria)

### DEFINITION

Scabies is a polymorphous dermatosis caused by the *Sarcoptes* or *Acarus scabiei*. The French name is "*gale*" but "*gale Bédouine*" is prickly heat, and "*gale filarienne*" is onchocerciasis. The old term "psora" means among other things also scabies.

### HISTORY

This skin disease has already been written about in times long past, in China and in Egypt, by Hindus, Greeks and Arabs (DUJARDIN). BERNARDINO RAMAZZINI (1633–1714) looked upon scabies as the filthiest of all diseases, in treating which even celebrated university professors could gain little or no honour, whereas, on the other hand, some ancient ointment out of an old book might perhaps effect a speedy cure.

### AETIOLOGY

The cause of scabies was discovered in 1697 by GIOVANNI COSIMO BONOMO and DIACINTO CESTONI and rediscovered in 1834 by SIMON FRANÇOIS RENUCCI.

The *Sarcoptes scabiei var. hominis* belongs to the arachnida. Its ovum is sleek, shiny and whitish, 168 $\mu$ long and 90 $\mu$ wide. During the life of the adult female, which may last for two months, over a hundred ova are laid at the rate of two or three in 24 hours. The eggs hatch in 72–96 hours and the larva passes through three immature stages in the case

of the female, and two immature stages in the case of the male. The time taken by a complete generation from egg through the various stages to the egg of the next generation, is at a minimum 14 days, and is usually more nearly 30 days. All stages in the life history dig into the skin, but none normally penetrates below the epidermal layer. EICHSTEDT, HARDY, MEGNIN, SILCERKIOLD and MELLANBY all maintain that the immature stages live mainly on the surface of the skin. HEILESSEN has shown that this is not the case. This apparent disagreement is due to the fact that only the adult females make extensive burrows. The other stages, which are of short duration, only tunnel for a limited distance. The adult male, however, probably makes quite extensive excursions. Under favourable circumstances, for instance when the host is asleep and the temperature and humidity under the bedclothes are high, the other forms may move about the surface of the body. Even the adult female, which usually remains in her burrow all her life, will sometimes leave the epidermis either because she is mechanically scratched out by the finger nails of the patient, or because local oedema makes conditions unfavourable, and she will then migrate to another locus. Experiments have shown that such a mite may wander from the left to the right wrist.

The intra-epidermal scabies-burrow or cuniculus—the typical, but not invariably detected symptom of scabies—is therefore caused only by the adult female mite. The burrow is extended at a rate of about two mm. a day. Soon after fertilization egg laying begins, and the ova are deposited in the burrow and are stuck to its lower surface. On hatching, the larvae leave the burrow; they dig into the surface of the skin, making small pockets, obtaining both protection and food in this way.

It has never been explained why scabies should affect certain specific sites in preference to others. And even the rash itself is hard to explain; the burrow is made by the mite, but the pathogenesis of the other generally papular rash is far more obscure.

It may be that the rash is due to hypersensitiveness of the skin to the scabies mite. The fact that re-infection with scabies should be marked by a shortened incubation period, a strong reaction of the skin and a smaller number of parasites, would appear to support this hypothesis. On the other hand, the results of the many sensitivity tests

made with the extract of the scabies mite do not clearly show that there exists in fact, such a hypersensitivity on the part of scabies patients. As things are, we can only conclude that the presence of the mite on or in the skin, with the resulting reaction of the patient, produces the clinical symptoms of scabies. This reaction is probably allergic in nature (MELLANBY· PRAKKEN and VAN VLOTEN)

The eczematization found to a high degree in some cases is caused by hypersensitivity to secondarily infecting bacteria and by scratching of the affected areas.

## EPIDEMIOLOGY AND SOCIAL SIGNIFICANCE OF SCABIES

Lower or higher frequency of scabies point to a—respectively—higher or lower social level of the population. A tremendous rise in the incidence of scabies has been observed during and after wars, even in countries not directly involved, but this has not been satisfactorily explained. It is probable that there are cycles of incidence unrelated to wars this view is supported by the fact that in Britain between 1930 and 1939 the incidence rose steadily in a period of increasing prosperity

The poor are generally more easily infected than the more comfortably situated not so much because of their uncleanliness, but rather because lack of living space often compels several members of the household to sleep in the same bed while the condition of the bed linen, etc. may also leave much to be desired.

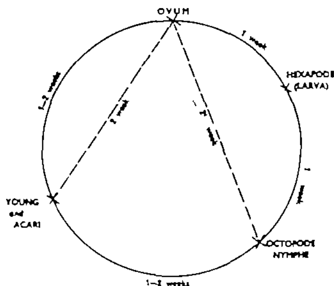
At all ages one may become infected, but younger people—up to 30—are more often infected than one might expect (BEEK)

In Europe, scabies is more frequent in winter than in summer (BRODIER POSEN)

Much has been, and is still being said and written about the manner in which infection takes place. As a general rule it may be said that scabies spreads from one individual—sometimes a symptomless sarcoptes carrier"—to another by the transfer of the mite. This may occur by direct contact between an infected and a healthy individual, *e.g.*, in bed. It would be wrong however to regard scabies as a kind of venereal disease rather is it a familial disease, in which intimate family contact promotes the infection.

It is clear that both direct contact and indirect, by the medium of fomites, can cause infection, but there seems little doubt that intimate

personal contact, particularly the sharing of a bed, is the most likely means of transmission. HEILESSEN has analysed data which suggest that as many as 16 per cent of cases may be due to such contacts as dancing. Several workers have demonstrated that the mite will survive at the temperature and humidity of the ordinary room for several days so it is clearly possible for bed clothes, for instance, to remain infective for that period. In a large series of experiments MELLANBY has shown that the risk of infection from wearing garments or using bedding recently in contact with scabies cases is less than 1 per cent. of the risk of




604 Scheme by SIMON

sharing a bed with the same patients. The disease may be transmitted venereally, but sharing a bed rather than sexual congress makes infection likely.

A follow up of over 5,000 cases in half of which the clothes and bedding were disinfested and in half of which this precaution was omitted showed a relapse rate of under 2 per cent. in each group. There was no evidence of a higher relapse rate in the over 2,500 cases where no disinfestation took place. This was responsible for the resolution of the British Ministry of Health in 1943 to the effect that — disinfestation

of clothing and bedding is unnecessary" GORDON and UNSWORTH have suggested that instead of "unnecessary" it would be better to say incommensurate with the expenditure of labour involved"

## SYMPTOMATOLOGY

The first manifestation of scabies is itching which becomes especially acute towards the evening One frequently hears that other members of the family—especially bedfellows—also complain of irritation. GOUGEROT even says that the bed fellow's itch may sometimes be the only symptom.

The lesions which sooner or later appear are polymorphous they include papules, vesicles, sometimes wheals, bullae, sometimes complicated by impetigo or other pyodermata. Especially in tropical countries scabies is nearly always accompanied by more or less marked impetiginization. Not frequent, yet almost characteristic of the presence of scabies, either at the time or in the past, is the moist eczema of the nipples and areolae in women who are neither pregnant nor suckling In children, impetigo of the buttocks, soles of the feet and between the fingers clearly indicates scabies

The real, typical symptom of scabies, which, however is not often found in adults, is the scabies burrow" Its presence is in fact, the proof of the disease but this is not to say that the burrow can invariably be demonstrated in every patient. This burrow appears like a short, irregular zigzag scale, which floats and looks as if it had been drawn with a needle. It may be filled with dirt (excrement?) in which case it forms a black zigzag line. HEILESSEN mentions as the principal sites of the burrows in women hands, sides of the feet (in Europe, especially among those who do not wash their feet) elbows (dorsal) axilla and breast (on and around the nipples) among men hands, phalanx, glans penis, scrotum, elbows, the anterior folds of the axilla, and navel. MELLANBY has shown that among over 900 adult male patients in Britain, over 60 per cent. of the burrows were on the hands and wrists, ten per cent. on the elbows, ten per cent. on the feet, ten per cent. on the penis and scrotum, and the remainder on other sites. On the penis lesions sometimes secondarily infected, are often found, but burrows containing living mites are less common than is often imagined.

The back is seldom affected in rare cases the burrows may be found in other places as, behind the ear under the nails etc.

Among chauffeurs mechanics etc. the lesions on the hands and wrists are rarely found, probably owing to the frequent contact with machine oil (MONTGOMERY)

To look for the scabies mite, which, despite the most thorough examination and diagnosis is not always found is as a rule, quite unnecessary and a time-consuming task. With practice, one may ad



605 Widespread scabies
*(Siemens–Leyden)*

mittedly become an expert in this search but for the G P working in more or less primitive conditions it would present too many difficulties and take too much time, though the ability to recognize the living mite in the skin is a great help Wrong diagnosis is undoubtedly common, and may account for as many as 30 per cent. of the apparent failures of efficient anti sarcoptic treatment It is far simpler and equally efficient to base the diagnosis on other phenomena. According to SIEMENS scabies is the only skin disease which may be diagnosed by its

localization alone. A rather frequent symptom, though of more academic interest than practical value, is a more or less marked eosinophilia. The duration of the irritation and the intensity of the eruption are more important than the number of parasites present (HELLESSEN)



606 Scabies of the heel as is often seen in children.

**ABNORMAL COURSE OF THE DISEASE**

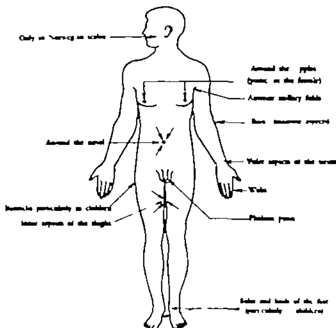
In children, scabies is marked by its localization about the footsoles, palms of the hands and buttocks. Burrows are often visible. Confusion with strophulus is always possible, especially when the child is the only scabies patient in the family as may readily happen if the child is being taken care of by neighbours and sleeps in their bed. In sucklings, the burrows are not infrequently seen on the baby's face (BUXTON JOHNSON MELLANBY)

The abortive form ("gâle des gens du monde") is marked by a lack of symptoms, the only ones being irritation and a few lesions in the most usual places (SIMONS and DOORNINK)

Scabies norvegica ("gâle croûteuse") may be found anywhere but appears to be more frequent in tropical regions. In this form, the skin is covered with dry greenish-grey squamous crusts pierced by many burrows, and filled with mites, ova and excrement. The affection is localized around the elbows knees, joints of the feet, the dorsal side

of the extremities, chin, cheeks, eyebrows and ears. Infection of the scalp usually leads to considerable loss of hair which may result in total baldness Pustules and infiltrates are found in addition to crusts. The affection sometimes resembles psoriasis (COVISA) at other times erythrodermia (BESNIER, JORDAN PAUTRIER) or again ichthyosis (GATÉ)

The numerous scabies mites found in the crusts differ hardly if at all, from the ordinary *S scabiei* and set up common scabies in other



607 Sites of predilection

*(S mons Amsterdam)*

individuals This contradicts FURSTENBERG s opinion which claims that a special small type of acarus is the cause of scabies norvegica.

This type of scabies is not always recognized as such, and may therefore—as has been repeatedly stated—be the cause of epidemics in hospitals The patient s general condition is usually rather low In most cases there is eosinophilia Scabies norvegica is found most frequently in individuals already afflicted with other diseases, leaving

them with low resistance, e.g. leprosy, tabes dorsalis (at times with exceedingly long burrows) syringomyelia, idiocy, trichophytia, favus, helminthiasis and general neglect.

The trouble begins with ordinary scabies, and often persists for many years with little or no irritation.

This disease is highly contagious, due to the large number of parasites present. It resembles animal scabies, where similar conditions obtain,



608. Scabies norvegica in the Negro
(Piers–Nairobi)

but nevertheless it does not seem to be caused, as some writers have suggested, by mites from animals.

## COMPLICATIONS

The most frequently found complication is secondary impetiginization. In many cases real furuncles are found, sometimes folliculitis and carbuncles. Lymphangitis, lymphadenitis and erysipelas are results of

a deeper penetration of the secondary infection. In some cases there is eczema caused by scratching, or a bacterial hypersensitivity (*cf.* also eczema post scabiem).

A few cases of true secondary sepsis after scabies in infants have been described (PICK, GATÉ and others).



609 Scabies norvegica in lunatic senile woman

Not infrequently nephritis is found in impetiginized scabies, especially among children and young people.

It used to be thought that scabies alone could cause albuminuria; later investigation, however, showed that the albuminuria had no direct connection with the scabies but was causde by the secondary nephritis referred to above.

The luetic primary lesion, or soft sore, is fairly often seen in skin lesions of scabies ("chancre galeuse"). GOUGEROT and BLUM have described a case of this kind, in which, moreover quite a few Spirochaetae pallidae were also found in other scabies lesions on the abdomen.

In some cases, even after proper treatment, there still remain some strongly irritating nodular infiltrations the size of a pea, and resembling prurigo nodularis These were first mentioned by AYRES and NELSON Histological examination showed a lymphocytous infiltration in the papillary the sub-papillary and centre layers of the cutis. Neither ova, excrement nor mites could be found in this infiltration, as was confirmed by painstaking examination (BEEK) (The therapy of this troublesome disease consists in the application of a strong tar ointment, *e g* pure ichthyol, electro-coagulation and scratching out.)

Skin diseases which resemble scabies—or *vice versa*—are, pruritus, post-scabies pruritus or dermatitis, pediculosis corporis, copra itch, dermatitis pratensis dyshidrosis impetigo and disseminated papulo vesicular eczema.

#### THERAPY

As early as 1867 LOCHNER wrote 'It should be very easy indeed to get a little cheap fame by discovering a new remedy against scabies And indeed, in contrast to what we find in other diseases where the number of remedies recommended is in inverse ratio to their therapeutic value, there exist a goodly number of remedies against scabies The pharmaceutical industry moreover has not failed to apply itself to producing these medicaments and to putting a number of specialities on the market, the best known being mitigal, sanigal, scabicidol, neo-scabicidol, duscabin, peruscabin, nonoscabin, etc.

(a) There are many medicaments which will cure scabies.
20–25 per cent. sulphur in a fatty base is the oldest reliable remedy
An elegant preparation has been described by POLANO *viz*.,

| | |
|---|---|
| cerea lanette | 30 |
| cetol extrac | 45 |
| aqua ad | 230 |

fiat cremor adde

a deeper penetration of the secondary infection. In some cases there is eczema caused by scratching, or a bacterial hypersensitivity (*cf* also eczema post scabiem)

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General rules to be observed in the treatment of scabies may be summed up in a few words

(i) the skin of the entire body with the exception of the face should be covered by the antiscabioticum

(ii) treatment of every infected member of the family as well as of those who might be infected, should be undertaken at one and the same time, even when the latter show no symptoms whatsoever.

Possible complications of the treatment are irritation, or the notorious post scabies dermatitis, which can be very obstinate. This may appear especially when all-too-prudent patients take several cures in succession, or bathe too often, because the irritation does not cease at once. In such cases a greasy ointment is indicated. We personally use, to this end, pasta zinci, 50 per cent. boric acid ointment, 50 per cent. and forbid the use of soap and water.

In some cases the dermatitis may assume the appearance of erythroderma. In one of our own cases this erythroderma was complicated by uraemia with a 2 g urea content of the blood, which brought the patient to periculum mortis

NITTO, FUHNER and BASCH observed, in some cases of breast-fed infants and babies up to two years, sulphur poisoning with raised temperature, vomiting diarrhoea and oedema.

A clear distinction should therefore be made between (a) scabies, (b) post scabies dermatitis, and (c) relapse of the scabies, whether complicated by post scabies dermatitis or not.

## HUMAN INFECTION WITH ANIMAL SCABIES

Animal scabies in man is rare but one hears of it now and then.

Many species of sarcoptes can pass from animals to man usually from cats or dogs, but the infection may be transmitted by other animals, *e g* horses (to their mounts or grooms) camels (to the riders of the camel corps) monkeys (to their keepers) lions (to the tamer), as well as by birds

Many so-called cases of scabies due to mites derived from animals are due to parasites other than *Sarcoptes* In these, no burrows are found the affection is quite transitory and is spontaneously cured as soon as the source of infection is removed. Infection from animals with sarcoptic mange is different. Here typical burrows may develop

but the race of *Sarcoptes* in such animals as have been studied, though morphologically so similar to man's form as to be indistinguishable, is evidentally biologically unsuited to live on man, and a few weeks after infection the infestation dies out and a spontaneous cure results (See also page 857.)

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CHAPTER 37

# URTICARIA MULTIFORMIS ENDEMICA

## (Harara)

A. DOSTROVSKY

Jerusalem

### DEFINITION

The word "Harara" is an arabic word which means "heat" and is used by the Arabs for several diseases. The term is applied here to an urticarial dermatosis caused by the bite of the phlebotomus

### HISTORY

The disease was first described by DOSTROVSKY in 1925 under the name urticaria multiformis endemica. Later HOFFMAN described harara in Cuba, and SZENTKIRALYI and LORINCZ in Hungary (1933) THEODOR (1935) published an experimental study on phlebotomus bites in relation to harara.

### EPIDEMIOLOGY

The disease appears during the hot season, from May until November and is endemic in Israel and surrounding countries.

Newcomers, the newborn, and un-immunized adult natives are generally attacked by harara. Usually the disease appears in members of the same family showing different degrees of violence on the one hand strong dermatological reactions and on the other hand few lesions may be present

### AETIOLOGY AND PATHOGENESIS

The peculiar localization of the disease on the uncovered parts of the body indicates an exogenous skin affection.

In spite of the individually different reactions, we have to attribute the disease to an insect bite, new to immigrants. Such an insect in our country is the phlebotomus papatasii which has been found in the homes of persons affected with this disease.

The symptoms represent different grades of an allergic reaction to the bites of the phlebotomus. A state of immunity remains after disappearance of the lesions after the first year or in one of the following seasons. New lesions in following seasons are generally smaller and their



610 Endemic urticaria bullosa from the bite of the phlebotomus known as harara

duration is shorter. In rare cases no resistance to the bites develops and the disease appears every season.

From the investigations of HECHT (1933) it is known that insect bites cause an allergic state of the skin which may be followed by an hyper- hypo- or anergic reaction. BOYCOTT in 1928 performed interesting experiments with phlebotomi. Five persons in England were exposed to bites of Phlebotomus: four persons showed no immediate reactions. The fifth who had an immediate wheal reaction, had been in the Middle East 10 years previously. A second stinging of these four

volunteers 7 to 12 days later led to a reaction in the new as well as in the old stings (reactivation).

THEODOR (1935) confirms in his experimental investigations that harara is caused by bites of phlebotomus papatasii and that the disease is based on a certain allergic status The interval between the first and second bites is the time required to develop an allergy These experiments explain the clinical observation of an exacerbation of elements 7 to 19 days after the beginning of the disease. This could be a hyper sensitive reaction to repeated fresh bites together with a reactivation of old bites

## SYMPTOMATOLOGY

Every patient gives the same history Only a few days after arrival in the country he begins to suffer from itching sleep is disturbed and painful sores appear on his skin.

On examining the patient, firm papules of a vivid red colour, varying in size and slightly elevated, are found, and signs of scratching may be noticed The distribution of the lesions is as follows the dorsal part of



611 Harara multiform ppearance wheals, blisters and crusts.

the hands, in a lesser degree the volar side of the wrists, extending to the dorsal part of the fore-arms and the upper arms leaving the cubital and axillary regions free

The same picture is found on the lower extremities. Especially affected areas are the dorsal parts of the feet, the region of the Achilles

tendon and the malleoli Less affected is the anterior aspect of the lower leg The thighs are rarely involved The number of lesions decreases proximally so that they are sparse on the upper parts of the extremities.

There are many lesions on the face, fewer on the neck and still



612. Papular harara.

fewer on the thorax. The rest of the body is not affected The skin between the papules is normal. Often only the upper extremities are involved

The primary eruption of an urticarial papule is not always present in the same form. Sometimes there is a tiny vesicle at the top as in strophulus. Often a sero-haemorrhagic crust is found or smaller and bigger vesicles with serous contents are present This serous fluid may become haemorrhagic and look bluish, especially in old people with high blood pressure

The vesicles are surrounded by a red halo They contain many eosinophilic cells and are microscopically and culturally sterile

The development of vesicles occurs only in sensitized patients

The morphological aspect varies As a rule the original picture is changed by scratching and infection into impetigo resulting in a picture of pyoderma with the localization as described above

The lesions are small in the first few days but after 7—10 days the patient shows numerous exuberant elements *e g* where in the beginning only small urticarial papules were to be seen, there appeared later

big papules or blisters All these different forms may be present in one and the same individual at the same time.

### CLINICAL SUMMARY

The disease is localized on the uncovered surfaces such as the face and exterior surfaces of the extremities. Symptoms are of various types a) papular urticaria like lesions which are hard, slightly elevated and of a bright red colour b) serous or haemorrhagic blisters c) lichen-like elements d) impetiginous lesions e) intensive itching

### DURATION

In the course of a few weeks the efflorescences become sparser less exudative and eventually disappear In the following year the disease either returns in a mitigated form or not at all.

### PATHOLOGY

Absolute and relative hyperkeratosis. Slight acanthosis There is a striking oedema in part of the papillae. Throughout the whole dermis there are infiltrations arranged in foci mainly around and along the blood vessels and appendages These infiltrations are composed of round cells large numbers of eosinophils, some histiocytes and polymorphonuclear cells

### DIAGNOSIS

In the differential diagnosis the following diseases have to be taken into consideration scabies, prurigo miliaris and lichen tropicus (prickly heat). Lichen tropicus is characterized by pinhead sized papules on a reddened skin and is localized mainly on the body on the flexor surfaces of the forearms, around the wrists and on the shoulders The patient suffers from an intense burning and pricking and in lesser degree from itching (This affection is caused by the swelling of the ducts of the sweat glands.) (See Chapter 32 Vol. I )

In urticaria multiformis large areas of skin between the lesions are normal in contrast to prickly heat. The differential diagnosis from strophulus is difficult, the more so because there are sometimes mixed forms and a provocation of strophulus by multiform urticaria.



613 Impetiginized hararа.

## THERAPY

As in all exogenous allergoses elimination, antipruritic drugs and desensitization are used. Five to ten ml of blood from immune patients were injected intramuscularly with good results. The same results could be obtained by autohaemotherapy. Antihistaminic drugs seem to alleviate the pruritus.

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CHAPTER 38

# TUNGIASIS

D. B. JELLIFFE

Ibadan (Nigeria)

## DEFINITION

An (Inflammatory) skin condition which is due to intracutaneous invasion by the gravid female sandflea (*Tunga penetrans or Dermatophilus penetrans*) (Chigger[1] chigoe, nigua, bicho do porco tomsico, migor) There is much confusion about sandflea (Tunga penetrans) and sandfly (Phlebotomus) (see also Vol. I footnote page 3).

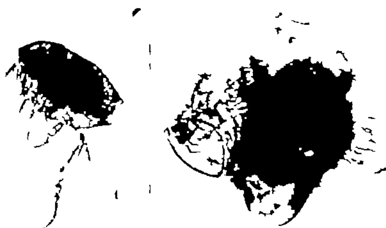
## AETIOLOGY

The males and unfertilized females live an independent existence in dry sandy soil, the dust and ashes of native dwellings and the refuse of cattle pens, chicken runs etc. They feed by sucking the blood of any available warm-blooded animal, particularly pigs, chickens and man.

Adult chiggers are brownish red in colour and slightly smaller than the common flea. As soon as the female becomes impregnated, she attempts to attach herself to any mammal or bird and burrows diagonally into the skin until only the posterior segment protrudes. When firmly embedded, and nourished by blood sucked from the host, ovulation takes place producing an enormous increase in the dimensions of the insect's abdomen, which becomes swollen to the

[1] According to Dorland's dictionary (20th ed.) the name *chigger* is given to the harvest mite or red bug (larva of the Trombicula irritans or alfreddugesi) and that of *jigger* or chigo(e) to the tunga penetrans.

size of a small pea. As soon as the eggs are ripe, they are ejected on to the ground, and develop into larvae, which pass through several moults. The young imago emerges on about the seventeenth day



614–615 Male and gravid female chiggers.



616 Tungiasis
([illegible])

## EPIDEMIOLOGY

Formerly confined to South America and the West Indies it is thought

that the chigger was probably first transported to the West Coast of Africa in a load of ballast sand in 1872. Since that date, it has spread to most of tropical Africa, including some of the adjacent islands. During the Abyssinian campaign of the second World War tungiasis was a common cause of morbidity among Indian troops. In addition, the flea has been imported into the West coast of the



617 Tungiasis multiple chigger pustules in honeycomb appearance.

Indian peninsular from East Africa and has spread as far inland as Karachi.

## SYMPTOMATOLOGY

In the early stages, the presence in the skin of the gestating female chigger produces irritation and a hard, itchy slightly raised red subcutaneous node, close inspection of which shows a central black dot produced by the plug formed by the flea s two posterior abdominal segments. Shortly after this, suppuration occurs and a pea-sized pustule is formed round the distended body of the chigger These pustules may be single or multiple, when they may be discrete or aggregated into solid plaques with a well-marked honeycomb appear

ance. As the flea is unable to jump more than three feet or so, chigger pustules usually occur beneath the toenails between the toes or on the soles of the feet. However any other part of the body may be attacked, including the external genitalia, the perineum, the buttocks the hands and the face, and this is particularly likely to occur in scantily clothed natives who may squat upon the ground.



618 Tungiasis of the buttocks aggregated chigger pustules (honeycomb plaques)

If the chigger is not removed, the surrounding suppuration increases and the flea is expelled when the pustule ruptures An infected pit like ulcer is left, from which cellulitis septicaemia, gas gangrene or tetanus may develop The last is commonly seen in Southern Nigeria and appears to be especially frequent in Costa Rica, where in a four year period, 250 deaths were reported from this cause In most untreated cases the ulcer slowly heals but occasionally develops into a spreading septic lesion of the tropical ulcer type

**PROPHYLAXIS**

a. *Foot protection* Shoes or ideally high boots should be worn, while a daily bath and foot inspection should be undertaken paying particular attention to the region of the nails BALFOUR recommends that an ointment containing 5 drops of liquor cresoli saponatus in 1 ounce of vaseline be rubbed into the feet thoroughly daily This method is said to protect for up to three days, while also killing any fleas that have already attached themselves.

b *Floor disinfection*. Camping, and particularily sleeping on the ground, in chigger infested areas especially in the neighbourhood of



619 Depigmented scars following multiple chigger pustules.

native villages, chicken runs and pig pens, should be avoided. Proposed camping grounds or resthouse floors may be swept or fired, if feasible. The floors of tents or huts may be sprayed or sprinkled with various insecticides, including flaked naphthalene, carbolic water pyrethrum powder DDT or gammexane. The inside of boots can be treated with a strong infusion of native tobacco

**THERAPY**

If detected before the flea has burrowed into the skin, it should be removed. If the chigger has embedded itself in its burrow it must

be extracted intact. The flea may be killed before removal by applying chloroform, ether turpentine or mercurial ointment to the skin. After preliminary cleansing the opening hole of the chigger pustule is



620 It is said that the Caribbean Indians have a needle pierced through their lips, because they have no pockets and they have their needle ready fo the removal of the tunga. Probably it is only for sake of beauty (cf earrings).
*(Simons–Amsterdam)*

enlarged slightly with a sterile needle. The intact insect can then be enucleated or may be expelled by gentle pressure. The wound is cleaned carefully and chemotherapy commenced if required.

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CHAPTER 39

# NUNEZ ANDRADE'S DISEASES

ROBERTO NUNEZ ANDRADE
Mexico City

## 1 NUNEZ ANDRADE DISEASE

### DEFINITION

This disease is a parasitic dermatitis caused by the bite of the larvae of *Neoschoengastia nunezi* Hoffmann 1944 It is characterized by molluscoid lesions and intense pruritus.

### EPIDEMIOLOGY

The disease is observed specially during the rainy season (June to September) it is more frequent in children. More than one hundred cases have been observed in Mexico

### HISTORY

This dermatosis was first described by Nunez Andrade, in 1944 in México City Hoffmann made the parasitological study at the Instituto de Salubridad y Enfermedades Tropicales of México (1944)

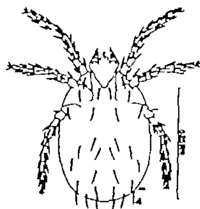
### AETIOLOGY

The disease is caused by the bite of larvae of *N nunezi* The larvae of *N nunezi* a parasite of poultry produce small petechia when the parasites are numerous they resemble "spots of ground brick"

### SYMPTOMATOLOGY

Nunez Andrade's disease is characterized by scarring molluscoid elements, vesicles, pustules and excoriations. The lesions are localized

on the scalp neck, back, axillae, and the postauricular folds especially. Swelling of the lymph nodes and intensive pruritus are common. Asthenia, anorexia, insomnia, and fever have been reported.



621 Neoschoengastia nunezi.

**DIAGNOSIS**

The condition should be differentiated from

1. Other trombidiasis
2. Molluscum contagiosum.
3. Scabies
4. Animal scabies.
5. Other acariasis
6. Gamasoidosis
7. Cimiciasis.
8. Tick dermatitis.
9. Pediculosis.
10. Puliciasis.
11. Tungiasis.
12. Haematosiphoniasis (Nunez Andrade)

**THERAPY**

Ointments with benzyl benzoate, alone or with DDT (Hexascabian S 107 Novascabian, Scabi Scabiol, Cabiol, Scabisan, Benzoped,



622. Nunez Andrade disease pustules spread over the shoulders, back and breast.



623 Nunez Andrade disease strophulus-like lesions.

Kwell, Benylate, Enbin, Gexane, Eurax, Benzochloryl, Antiscabia, Detebencil).

If secondary infection is associated application of gentian violet, 1 per cent.

Abscesses should be opened.



624 Nunez Andrade disease pustules on the scalp

**PROPHYLAXIS**

Since *N. mexicana* is a parasite of poultry DDT should be used in the fowl houses.

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## II HAEMATOSIPHONIASIS

### DEFINITION

Haematosiphoniasis implies the cutaneous lesions caused by the bites of the *Haematosiphon inodora* Duges 1892. The native name is chinche de los gallos (chicken bug) or coruco

### EPIDEMIOLOGY

*H inodora* is a parasite of poultry It is found everywhere in the Mexican Republic, living on poultry and humans after taking a full supply of blood it abandons its host to go and hide between boards, cracks in the wall, bed clothes and other places



625. Haematosiphon inodora.

### HISTORY

This dermatosis was first described by NUNEZ ANDRADE in Mexico City in 1945 when hundreds of cases were observed.

### AETIOLOGY

*H inodora* commonly called "*poultry chinch*" is an insect 5 mm long and 3 mm wide, having a red-greenish colour the body before feeding is flat and becomes rounded after having sucked blood.

### SYMPTOMATOLOGY

Haematosiphoniasis is a polymorphous dermatitis forming wheals papules vesicles, pustules scabs and small linear scars It is accompanied by intense pruritus burning pain, general malaise, insomnia and fever due to secondary infection Generally it is localized on any part of the skin, but specially on the limbs and the uncovered parts. Formation is in groups of twos, threes, or fours, almost always in zig zag formation.



626 Haematosiphoniasis eroded vesicle on the lower leg

### DIAGNOSIS

The condition should be distinguished from

1 Other cimiciasis.
2. Mosquito bites, bee stings bites of ticks or other flies.
3 Pulicosis
4 Human or animal scabies
5 Other acariasis

6. Pediculosis.
7. Common and papular urticaria.
8. Nunez Andrade's disease

## THERAPY

Consists of relieving the pruritus with anti-pruritic agents if a secondary infection is present, Dalibour water application of gentian violet (1 per cent) or iron subcarbonate ointment (1 part in 30 of petrolatum) may be effective For extensive infection penicillin may be used.

## PROPHYLAXIS

There is need for the eradication of the parasites from infested build ings, by the use of insecticides such as DDT

## REFERENCES

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# ARTHROPODS AND OTHER ANIMALS IN RELATION TO DERMATOLOGY

P. H. VAN THIEL

Leyden

In this chapter arthropods and other animals will be enumerated which, by bite, sting or other contact, cause pathological reactions in the human skin.

They are

| | | |
|---|---|---|
| A. Hexapoda or insects | 1. | Nematocera (mosquitoes and mosquito-like animals) |
| | 2. | Brachycera (flies and horse flies) |
| | 3. | Hemiptera (bugs) |
| | 4. | Siphonaptera (fleas) |
| | 5. | Anoplura (lice) |
| | 6. | Hymenoptera (bees and wasps) |
| | 7. | Lepidoptera (bees and wasps) |
| | 8. | Coleoptera (beetles) |
| B. Arachnida or spiders | 1. | Acarina (mites) |
| | 2. | Araneida (spiders) |
| | 3. | Scorpionida (scorpions) |
| C. Chilopoda (centipedes) | | |
| D. Other animals | 1. | Coelenterata (jellyfish, polyps, corals and sea anemones) |
| | 2. | Mollusca (shellfish) |
| | 3. | Hirudinea (leeches) |
| | 4. | Pisces (fishes) |
| | 5. | Ophidia (snakes) |

Some parts of this chapter are quoted from Ph. Manson Bahr: Manson's Tropical Diseases, or from the Manual of Tropical Medicine, of the National Research Council of U.S.A.

Affections caused by Helminths are not included in this chapter.



1 Simulium reptans



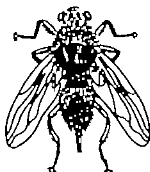
2. Tabanus nigrovittatus



3 Chrysops silaceus



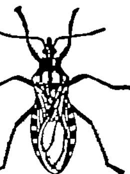
4 Stomoxys calcitrans



5 Hypoderma bovis



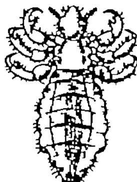
6 Cimex lectularius



7 Rhodnius prolixus



8. Pulex irritans



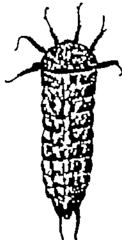
9 Pediculus humanus



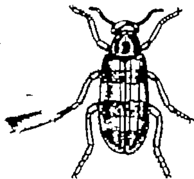
10 Phthirus pubis



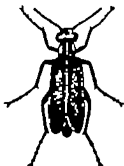
11 Vespa crabro



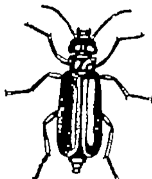
12. Megalopyge opercularis



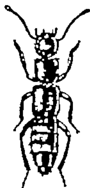
13 Mylabris cichorii



14 Epicauta marginata



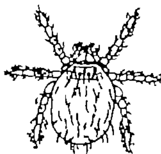
15 Lytta vesicatoria



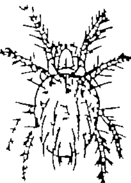
16 Paederus apec



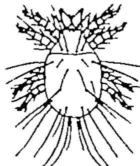
17 Cerapterus concolor

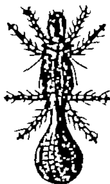


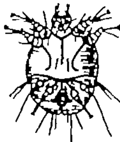
18 Trombicula akamushi

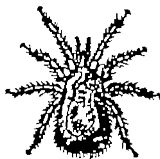

19 Tetranychus pacificus


20 Cosmoglyphus krameri

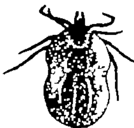

21 Tyroglyphus longior var castellani

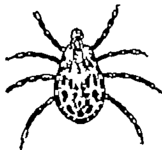

22. Pyemotes ventriculosus


23 Sarcoptes scabiei


24 Dermanyssus avium


25 Demodex folliculorum


26. Ixodes ricinus


27 Dermacentor andersoni

**A. HEXAPODA (Insects)**

1 Nematocera (mosquitoes and allied families, charactenzed by long threadlike antennae consisting of at least 6 joints on the head Only the females feed on blood).

a. *Culicidae* (mosquitoes). The female feeds on blood through its long, delicate mouth parts, either directly from a capillary or from a pool of extravasated blood (GORDON and CREWE). This has been studied by HECHT and afterwards by GORDON and CREWE, in *Anopheles maculipennis* and in *Aëdes aegypti* The skin may react to the injection of the salivary fluid.

(i) only by an *immediate primary wheal reaction* the erythema and oedema spreading peripherally This type of reaction is restricted to a minority of individuals.

(ii) In some cases a *delayed or secondary reaction* is seen, following this evanescent, immediate reaction, after about 6 hours (sometimes not until 36 hours afterwards) and growing much larger the next day it may not disappear until some days later on the dark skin local pigmentations may follow

(iii) A *primary papular reaction*

(iv) *Delayed papular reactions* without any primary wheal reaction, sometimes after a latent period of 1–7 days

A person reacting only with delayed papules may also show immediate primary wheals on the spot where prior to a mosquito biting, serum from an individual reacting only with immediate wheals is injected into his skin (Prausnitz Kustner s test) This proves the wheal reaction to be allergic.

Whereas irregular exposure to mosquito-bites may produce and maintain the immediate reaction, the evidence of individuals exposed to mosquitoes for many years, either in the tropics or in other countries shows that irregular exposure over long periods is followed by the disappearance of the delayed reaction. This experience suggests that this delayed reaction, which appears independently of previous exposure to the bites of the insect concerned, is due, not to sensitization, but only to the effect of the injection of a slow acting poison produced by the salivary secretion (GORDON and CREWE).

The immunity" to mosquito bites shown by natives of all ages in the tropics is not a racial characteristic, but is due to the fact that from birth they are regularly exposed to the bites of these insects *i.e* a process of de sensitization. It is probable that other Culicidae cause similar reactions.

b *Psychodidae* (sandflies). These are minute hairy flies (1 5–2.5 mm in length) Apart from causing leishmaniasis (vide V 1 I chapter 11), the phlebotomus may also set up urticaria, a described in chapter 37 on Harara

c. *Chironomidae* (' merutus agas etc ) Culic ides Ceratopogon, Leptoconops. They are very small (1–3 mm long) slender bloodsucking gnats, generally known as midges. In biting habits they resemble Simuliidae.

They can pass through the meshes of a mosquito net. The female bites man viciously frequently at dusk or night fall, but in Europe by day also. The bite causes considerable itching, and wheals which appear either at once or after a day or two Repeated bites for some months may be followed by a certain immunity or at least tolerance.

d. *Simuliidae* ("jinja "poty" "pipse fly" "akaran "buffalo gnat" "black fly"). Generally small (1–5 mm long), dark, bloodsucking insects resembling small flies, with short mouth-parts. Characteristic is the prominent hump caused by the strong development of the scutum and reduction in size of the prescutum. The antennae are composed of ten or eleven joints. The wings are broad and iridescent. Females feed by day on mammalian blood. The bites are painful. The female s bite causes topical phenomena—erythema resembling erysipelas and oedema, adenitis, and, often also, systemic disturbance.

2. Brachycera (flies and horse-flies).

To be distinguished from Nematocera (sub 1 above) by their antennae, usually consisting of 3 joints.

a. *Orthorrhapha*. Tabanidae (horse flies, clegs, deer-flies, gad flies).

Tabanus Haematopota, Chrysops. The antennae are not located in a frontal groove. The proboscis is on the front of the head. They are strong fliers which readily attack man, and resemble large flies. The proboscis of the larger flies is too bulky to enter the lumen of capillaries and is used to suck up the blood which results from repeated laceration of small subcutaneous vessels (GORDON). Only the females suck blood.

Some individuals do not react to the bite of these insects others do immediately and violently in particular probably sensitized persons. The bites cause local haemorrhages in the skin.

b. *Cyclorrhapha* (flies).

Frontal groove around the bases of the antennae. Bloodsucking flies (both males and females) are Glossina (tsetse fly), and the cosmopolitan *Stomoxys calcitrans* or stable fly The proboscis sticks out straight forward. The bite is painful. GORDON and CREWE observed that Glossina feeds from a pool of extravasated blood.

Far more important for the human skin are the flies which cause myiasis (see chapter 48), and which include Oestridae (bot-flies).

In some parts of Africa the larvae of *Auchmeromyia luteola* visit natives sleeping on mats on the floor, suck their blood, and then retire to cracks in the huts.

3. Hemiptera (bugs)

a. *Membranacei* (bedbugs)

The body of Cimex, 4.8 to 8.4 mm long is broad and flat the head

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parts adapted to sucking blood Both sexes feed on blood. The larva is a footless maggot of a whitish colour, which feeds on debris crumbs and faeces of the adults.

*Pulex irritans* is the common human flea. Dog cat and rat fleas readily attack man.

HESCHELES studied the flea bite in children 2 to 12 years of age. While the fleas were sucking blood, a reflectory erythema occurred in a number of cases followed after a few minutes by a hyperaemic haemorrhagic macula (roseola pulicosa), which gradually disappeared, and became discoloured leaving the next day purpura pulicosa. PAWLOWSKY and STEIN studying sections of the skin after injection of the flea's salivary glands, observed dilatation of vessels (hyperaemia) and perivascular infiltration, with slight oedema at the periphery

Other children showed urticaria surrounded by a red areola (maximally after 10 to 15 minutes), which disappeared leaving an erythema.

HESCHELES did not succeed in obtaining a changed type of reaction by repeated flea bites in persons reacting with urticaria. CHEANEY WHEELER and REED, and afterwards MCIVOR and CHEANEY succeeded in desensitizing persons against the bite of human- dog and cat fleas. The desensitization may last a few months to some years but frequently there is no "immunity" produced whatsoever. Diluted saline solution extractions of dried fleas produced after some 6 injections in adults in the course of 2–4 weeks smaller urticarial papules lasting for a shorter time, and causing less pruritus. This improvement sometimes lasted 2–3 months in other cases permanently

b. *Tunginae* (sandfleas)

*Tunga* (*Dermatophilus Sarcopsylla penetrans* or "chigoe"). These are fleas with a special mode of development, and a sharp rostral prominence (see chapter 38)

5 Anoplura (lice)

a. *Pediculi capitis hominis* and *corporis* (*vestimenti*) are obligatory parasites of man. They have flattened bodies and are wingless. Their development is direct the larva and nymph resembling the adult and feeding on blood.

The site of the bite is usually seen either as a small haemorrhagic spot which later turns a bluish red, or as a papule surrounded by a hyperaemic zone usually there is little or no urticaria.

Excessively frequent biting causes morbus erronum or "vagabond's skin revealing diffuse pigmentation, lichenification, scratches, and pyoderma. In the tropics, where *Pediculus vestimenti* is rare, this affection is practically unknown.

Injection of the insect's bean-shaped salivary glands first set up a primary urticaria, which soon disappeared, being followed, 8–12 hours later by an itching papule which lost its colour only after 3–4 days. Anatomically the Malpighian layer was found to be locally necrotic, with cellular infiltration.

In regions seriously infested with lice the inhabitants tend to become tolerant, if not actually immune to their bites.

b *Phthirus pubis* (crab louse, pubic louse). It is distinguished from other lice by its broad, flat body and festooned abdomen. It lives chiefly on the skin in the genital and inguinal regions but may also be found on the eyelashes, eyebrows and, in children, on the hairs at the edge of the forehead.

Differential diagnosis as between this louse and the larvae of ticks lice may be recognized by the second and third pairs of legs having massive, talon-like claws.

Phthiriasis produces severe itching in the genital (sometimes also in the anal and axillary) regions sooner or later pseudo-crusts are found, these being the lice, which are strongly attached to the skin. Being transparent, they show a pseudo-mimicry (SIMONS) and are coloured to resemble the colour of the skin, except after sucking blood, when they are black. Phthiri do not cause disease, although in some cases bluish maculae may be seen (maculae coeruleae) This discoloration is due exclusively to the excretion of the insect s salivary glands it is also found in blood-agar plates after injection of the same excretion. It is probable, therefore, that the saliva *impregnates the skin evenly over the area of injection*, so producing a bluish-green colour the nature and composition of which have not yet been identified.

## 6 Hymenoptera (bees and wasps)

Bees and wasps have two pairs of wings and cannot therefore be confused with either bot-flies (Oestridae) or horse flies (Tabanidae), which have only one pair of wings. The sting—a specialized ovipositor (that of *Vespa cabro* is 3 5 mm long)—is pushed into the skin, and through it the poison (apitoxin) is introduced. This poison contains formic acid from the large gland, and an alkaline neurotoxin substance (sapotoxin- or cantharidin like) from the small gland. Separately they would produce only a weak reaction, but in combination, they constitute a violent stimulus the reaction being distinctly acid. It might, therefore, be thought that alkaline compounds *(ammonia, bicarbonate of soda) should have a neutralizing effect* according to FLURY however the alkalic component in the poison is the most toxic, so that acetic acid would be the therapy indicated. Anyway it will be obvious that local applications have little more than a symbolic significance in respect of the spontaneous, evanescent immediate reaction. The bumble bee s poison is less dangerous The bee s sting easily breaks off bumbles and wasps do not leave their sting in the wound, whereas the honey bee does.

In the case of a mild sting there is local swelling in the affected part sometimes coupled with pain, nausea, slight fever and a little itching The moderately serious form is the syncopal, with vertigo rigor and often excessive urticaria. In sensitized individuals there may occur a degree of (even

lethal) anaphylactic shock as the result of a single sting. Greatly feared is the sting on the mucosa of the mouth, tongue, or pharynx through eating fruit with wasps in it, when oedema may cause the patient's death from asphyxia.

The skin lesions produced by *Apis mellifica* include oedema and cellular infiltration, these changes being followed by a "walling-off" of the damaged tissue by a "palisade" of inflammatory cells (GORDON and CREWE).

Sufferers from asthma, migraine, and urticaria appear to be particularly liable to strong reactions. Haemorrhages in the skin and mucosae have also been observed.

When the sting has been left in the wound, it should be removed by pressure and tincture of iodine be applied. In serious cases, intravenous or intramuscular injection of an antihistamine preparation, 10 ml of a 10 per cent. solution of calcium gluconate, or coramine combined with a haemostatic agent (LECLERQ) may be needed.

Active immunization of persons such as bee keepers occurs from repeated stinging; it may also be produced experimentally.

7. Lepidoptera (butterflies, and moths) are characterized by the presence of numerous hairs on the body and wings. Except for a few wingless forms, two pairs of wings are present. The larvae are called caterpillars.

Several groups of caterpillars bear hairs capable of irritating the skin and mucous membranes. These hairs may either be simple bristles, sometimes provided with barbed hooks, or heavy hollow spines, associated with poison-secreting cells or glands. The skin of persons attacked by such caterpillars is pierced by these hairs with irritating effect. At first there is burning pain, followed by itching. The affected area develops whitish papules which soon become red. There may be nausea and fever, with numbness and swelling of the affected part. The finer hairs may occasionally become detached and carried by the wind, set up a painful conjunctivitis.

In the United States, thousands of cases of dermatitis caused by the hairs of *Megalopyge opercularis* (the "puss caterpillar") have been known to occur in a single season.

In Indonesia the "ular bulu" *i.e.* the larva of *Plecua fulvicollis* which occurs in the soil of tea estates, is said to cause a skin eruption on the feet; according to DAMMERMAN, however, this assumption is incorrect. On the tea-plants themselves caterpillars (Limacodidae) are found which, on contact with man, may set up dermatitis.

The hairs of the browntail moth caterpillar, *Euproctis phaeorrhoea*, produce a severe vesicular dermatitis called "browntail rash".

Persons who frequently come into contact with these hairs may become sensitized.

Maybe there exist primarily toxic hairs of caterpillars, and others which do not act strongly in man until after sensitization.

Another well known species is the gipsy moth (*Liparis dispar*) The caterpillar of *Dicranura vinula* squirts formic acid from its glands

For prophylaxis all bedding and clothing contaminated with the hairs should be thoroughly washed. Caterpillars may be destroyed by spraying trees and shrubs with a mixture of arsenate of lead, 7 lbs and dehydrated lime, 4 lbs to 150 gallons This concentration is needed to kill the cater pillars quickly otherwise they crawl about before dying shedding hairs wherever they go Workmen engaged in control work should wear protective goggles.

8 Coleoptera (beetles)

Typical beetles have two pairs of wings the front pair of which are modified to function as wing covers which are hard and horny in most species and meet in a straight line down the back The second pair of wings, which are folded beneath the first when not in use, are in most cases membranous. The metamorphosis is indirect, *i.e* the larvae, which change into the pupal stage, do not resemble the adults.

a. *Meloidae* (species of Epicauta in America and of Mylabris in Africa) contain cantharidin as a toxic principle. Accidental crushing of beetles in a field may lead to vesicular dermatitis. *Lytta* (*Cantharis*) *vesicatoria* the "Spanish fly" of Europe, was formerly used as a blistering agent.

b. Many species of *Staphylinidae* ("rove beetles") also contain a substance with irritating and vesicant properties. Blistering does not occur until a day or two after contact. As these beetles feed upon dead animal matter they may convey infection.

Species of Paederus cause, in many tropical regions, suppurant inflamma tions which are difficult to cure. The skin affections thus caused sometimes assume an epidemic character in both tropical and moderate climates.

c. *Paussidae Cerapterus concolor* a night-flying beetle of South-East Africa, harbours a highly toxic substance which causes blisters when the insect is crushed on the skin. Treatment is symptomatic. Soothing antiseptic lotions of a mild alkaline composition are usually recommended.

Arsenate of calcium or of lead (one oz to a gallon of water) is recc mmended for spraying the vegetation on which these beetles feed.

**B. ARACHNIDA (Spiders and kindred insects)**

In contradistinction to Hexapoda (sub A above) which as adults ha e 3 pairs of legs, Arachnida adults and nymphs have 4 pairs, the larvae, however 3 pairs of legs.

1 Acarina (mites)

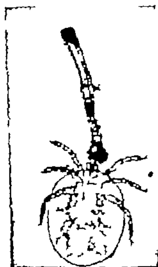
Mites are microscopically small animals whose cephalothorax and abdomen are hardly if at all, separated from each other

a. *Trombidiidae* (chigger mites)

They are minute, orange red mites just visible to the naked eye. The

adults and nymphs are not parasites of man, but live in the soil. The nymph and adult measure about 0.6 mm and have a peculiar figure-of-eight shape, with abdominal constriction. The larvae (sometimes called microtrombidia) which emerge from the eggs deposited in the soil, attach themselves for a day or so to the human or animal skin, where they feed and set up the histopathological changes described in Chapter 1 Itching sets in between 10 and 18 hours after the larva has attached itself. The itching ceases after 4–5 days. The larvae resemble minute larval ticks, but bear many bristles and minute plumose hairs on the back and legs.

"Harvest mites" are the larvae of *Trombicula autumnalis* in Europe. They



628. Trombicula batatas, larva with histosipho

are normally parasitic on moles and hares when parasitic on man they cause intensely itching and purpuric blotches. There is no sharp line of distinction between the harvest mite and the chigger mite the *latter is more particularly the larva of Trombicula irritans*—widely distributed in America— but the numerous species of Trombicula might well be indicated under one and the same name. They may become a veritable plague locally They are called by different names in different localities (*e.g.* "patatta losso" in Surinam (see Chapter 1 p. 142). The latter do not transmit disease to man but other species (*e.g. Trombicula akamushi deliensis* etc.) transmit scrub typhus. The mites attack men working in fields, causing minute necrotic ulcers.

After the mites have fed on the skin they fall to the ground, so that one

can only mitigate the itching, and counteract secondary infection caused by scratching.

For prophylaxis clothing should be saturated (preferably) with dibutyl phthalate, or with (less effectual) dimethyl phthalate.

b. *Tetranychidae* (red spiders)

This family comprises mites with slight hairgrowth, and stiletto-shaped mouth parts. They infest vegetation, and are known as the "Bicho Colorado" in South America.

Persons employed in picking hops often complain of the itch produced by this mite. In South Africa the adult mites are said to cause a kind of "creeping eruption" The tracks made in the skin are 0.33 mm in diameter The mite and its eggs may possibly be demonstrated at the end of the burrow

c. *Tyroglyphidae*

Microscopically small mites with many long hairs unstriped body and relatively slender legs. They are found on human food such as cheese, flour sugar etc. *Tyroglyphus farinae siro* and *longior* and *Glyciphagus domesticus* are causes of "grocer's itch" *Tyroglyphus* (*longior* var.) *castellani* and *Cosmoglyphus krameri*[1] copra itch and *Rhizoglyphus parasiticus* dermatitis of the feet in workers on tea estates.

It is probable that all these occupational dermatoses are of an allergic nature. When a certain degree of sensitization is reached, contact with only a few mites is probably sufficient to produce the symptoms. That it is a mistake to regard *Tyroglyphus castellani* as the exclusive provoker of copra itch is evident from LAARMAN's finding that another mite, *Cosmoglyphus krameri* (see footnote again) was observed in copra, and that there was a causal relation between the presence of this species and the copra itch of dock labourers who had been unloading a cargo of copra at the Port of Rotterdam (see Chapter 1 p. 68)

d. *Tarsonemidae* An observation at Cayenne has led to the opinion that Tarsonemus sp can burrow a track into the human skin.

"Grain itch" a violent dermatitis may be caused in farmers strawboard factory workers dock labourers and others handling cotton and crops by *Pyemotes* (*Pediculoides*) *ventricosus* which is found in cotton, cereals straw etc. It is an ectoparasite of the larval forms of many soft bodied insects. The abdomen of the pregnant female is swollen with eggs in it the eggs hatch and the young complete their development. Both male and female mites are sexually mature at birth. The males remain on the mother's abdomen, usually clustered about the genital orifice, but the females may feed on man and inject an irritating substance.

The characteristic cutaneous lesion is a rosy red wheal, surmounted by a vesicle which rapidly becomes a pustule. The wheals normally appear

[1] This mite illustrated in Chapter 1 p. 68 is there erroneously called "Carpoglyphus o[illegible]

10–16 hours after exposure, reaching their maximum development in about 24 hours. Because of the intense pruritus, the lesions are often excoriated and secondarily impetiginized Any part of the body may be attacked. Systemic symptoms which may accompany the eruption are fever, chills, malaise, nausea, vomiting and asthma. The dermis is slightly oedematous but the blood vessels and lymph spaces are not markedly dilated. A perivascular infiltration is present. Antipruritic treatment (*e g* lotion of water and vinegar, or an alcoholic solution of picric acid), and prevention or elimination of secondary bacterial infection are usually satisfactory

Prophylaxis Local application of miticides —sulphur benzyl benzoate and γ-benzene hexachloride the use of sulphur impregnated clothing Early bathing and change of clothing after a known exposure are obvious precautions.

e. *Sarcoptidae* (mange mites)

*Sarcoptes scabiei*, causing scabies They are microscopically small mites with fine, transverse grooves, close together on their body The legs are reduced to tiny articulated stumps. See Chapter 36

Human infections with animal scabies

In animals, mange is caused by the genera Sarcoptes Psoroptes, Chorioptes and Notoerdes. Only the genus Sarcoptes burrows into the skin the other genera live on the skin surface. "Mange" in man, caused by either Psoroptes or Chorioptes, has not been proved with certainty Species of Sarcoptes occurring in animals are indistinguishable morphologically from *Sarcoptes scabiei* They are given the epithets var *equi bovis canis cati ovis caprl, cameli*, etc., according to the animals on which they are found.

Many of these parasites can pass from such animals to man and cause dermatozoonoses Most of them probably do not burrow into the human skin, and they disappear again fairly quickly as soon as the source of infection has been removed but some species, it appears, do penetrate man s skin. This point has, so far been insufficiently investigated. For the rest, animal scabies" caused by them in man manifests itself on the skin by local pruriginous eruptions, often in the form of a papular exanthema, which may also spread to the arms, trunk and legs. Absence of mites proves the allergic character of the affection.

The Sarcoptes mites of animal origin often attack parts of the human skin, other than those considered as predilection sites of the human scabies mite for instance, the head. Infection may also be transmitted to man through objects in regular contact with animals such as harness, brushes cloths, etc. Such transmission is far less frequent in the case of human scabies. Transmission of Sarcoptes mites from animals to man is furthered by the fact that, after the death of the animal, these mites leave the gradually cooling corpse.

*S scabiei* var *equi* readily transfers itself to man. During the war, army units, owing to defective hygienic care, were frequently troubled with

"cavalry man's itch" BESNIER and MÉGNIN (cited by BRUMPT) believed they observed a formation of crusts resembling *scabies norvegica* but with a much more acute course. The nails were not involved. In a case described by DARIER (cited by BRUMPT) the syndrome resembled generalized pityriasis rubra. Mites were demonstrated in their thousands in scabs and crusts.

*S. scabiei* var. *bovis* quite readily transfers itself to man. Very often veterinary surgeons and all the inhabitants of a cattle farm may become affected. The itching is sometimes almost intolerable. In most cases treatment effects a rapid cure.

Scabies caused in dogs by *S. scabiei* var. *canis* is somewhat infectious to man; usually, however, the affection disappears spontaneously.

Far less serious for man is *S. scabiei* var. *cati* (also known by the name of *Notoedres cati*) of the cat. This affection almost invariably disappears after a fortnight. Veterinary surgeons treating small domestic animals, and their ancillary personnel regularly run a risk of contracting animal scabies from either dogs or cats.

Sheep's mange (caused by *S. scabiei* var. *ovis*) is, to man, hardly a menace. A much more notorious species, especially in the tropics, is *S. scabiei* var. *caprae*.

Camel's mange (*S. scabiei* var. *cameli*) may be transmitted to camel drivers etc. Keepers in zoological gardens may contract animal mange from lions, foxes, monkeys, llamas, kangaroos, etc. VAN DER ZIJL and HAGA have described a case of scabies in a boy who had contracted it from his pet monkey. This infestation presented itself as a scabies norvegica. The crusts crawled with sarcoptes mites. The monkey also showed crusts on its skin, in which mites were found.

Sarcoptes do not live on birds.

f. *Gamasidae*. They are fairly large mites, to be distinguished from ticks (Ixodidae, sub h below) by having their respiratory openings (stigmata) behind the third pair of legs and not, like the ticks, behind the fourth pair. The skin is hard (as that of the ticks), slightly if at all hairy; the legs are placed close together at the front half of the body.

*Dermanyssus avium* (*gallinae*) is the "bird louse", which sucks the blood of birds and infests birds' nests. When the birds leave their nests the mites may get into houses in the neighbourhood and attack human beings giving rise to a blotchy or papular erythema. The mites are not found on the body in the daytime.

g. *Demodecidae*.

*Demodex folliculorum*. This is a minute acarid, 0.3–0.4 mm long, with a long-drawn abdomen. Larvae and nymphs have 3, adults 4 pairs of legs. This mite is found in sebaceous glands and hair follicles or—relatively rarely—in blackheads or acne-pustules. It does not usually produce any symptom; at most it may create conditions giving rise to secondary

bacterial infections and, thereby to follicular and perifollicular inflammatory processes.

Transmission of Demodex mange from dog to man does not occur

b. *Ixodoidea* (ticks)

Ticks are large, blood-sucking Arachnoidea. The mouth-parts, which are adapted to biting, are provided with hooks that can be pushed out sideways, and by means of which the insect may become so firmly anchored in its victim's skin that its capitulum is torn off when removed by force. *This may lead to inflammatory symptoms, for which reason it* is advisable to kill the tick while in the skin, for instance by stopping up the tracheal opening, behind the last pair of legs with a fatty substance. Adults and nymphs have 4 pairs of legs larvae, 3 pairs. On the last extremity of the legs there are two claws, and sometimes a sucking disk (pulvillus) These distinguish larval hexapod ticks from the above described crab louse. The females are invariably larger than the males. The shell is often ornamented.

*Argasidae* (soft ticks) are distinguished from Ixodidae (see under) by the absence of a shield" (scutum) on the back. The mouth parts are situated ventrally Some species are found among the vermin in human dwellings, and visit man only to suck blood.

Species of Argas attack poultry and only rarely man. Some species of the genus Ornithodorus maintain much closer contact with man. No special affections caused by their bite are known, but *A. persicus* has been suspected of transmitting the Persian form of relapsing fever

*Ixodidae* (hard ticks). Mouth parts protrude in front of the body The body is covered by a scutum which, in the males, covers the whole of the back, but in the females only the part immediately behind the capitulum.

Both the females and the males suck blood, and sometimes stay fixed on the host until the female's eggs are mature. Eggs deposited in the soil produce larvae which settle on grass blades, etc., and wait until they can attach themselves to some passing person or animal. Some species of ticks pass through all the stages of their metamorphosis on one and the same host others require a different individual for each successive stage still others live, as larva and nymph, on one, and as adult, on a second individual MILNE, in a recent study has described that *Ixodes ricinus* passes practically the whole of its three years of life on the ground spending only three weeks on hosts.

During bloodsucking the skin becomes necrotic around the site of the bite.

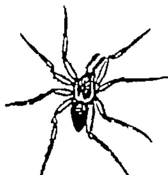
All species of ticks that are usually found only on animals may also be parasitic on man. This is particularly known, of the above mentioned *Ixodes ricinus* (the sheep- dog or wood tick), the Rhipicephalus and Amblyomma.

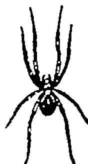
Dermacentor species transmit, in the United States and Canada, Rocky Mountain spotted fever

2. Araneida (spiders)

Cephalothorax and abdomen are superficially unsegmented the head may be superficially separated from the thorax by a groove. The venom is discharged at the tip of each of the chelicerae. Very few species have fangs powerful enough to pierce the human skin, or venom potent enough to produce more than a transitory local irritation when introduced into the skin. Even most species of large hairy tarantulas are innocuous, and at most produce only temporary discomfort.

Dangerous to man in the tropics are the relatively small species of Latrodectus (including the coal black "black widow" or "shoe button"





629 Lycosa tarantula Latrodectus mactans

spider of America, *L. mactans* with its orange or scarlet markings) *Lycosa* and *Ctenus*

When human beings are bitten by harmful spiders the insects inject toxin into the skin. At the site of the bite there is a small red spot with the marks where the two chelicerae have penetrated the skin a sharp pain, with little or no swelling, soon develops, and the area eventually becomes red and swollen. The whole limb burns and aches severely Systemic symptoms may follow Local necrosis at the site of the bite is at times suggestive of tropical phagedaenic ulceration or dermal leishmaniasis In some localities there is a record of 5 per cent. mortality as a result of Latrodectus venenation.

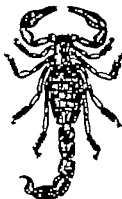
Therapy A tourniquet should be applied as soon as possible above the site of the bite the wound should be sterilized with tincture of iodine incised and suction applied. Injection of antivenin as soon as possible Later hot baths and intravenous injection of 10 ml of a 10 per cent solution of calcium gluconate to reduce the pain.

### 3 Scorpionida (scorpions)

They are characterized by large pedipalps terminating [illegible] claws; the cephalothorax is unsegmented; the abdomen is divided [illegible] anterior portion and a narrow posterior portion, with a [illegible] extremity ending in a curved sting with which they pierce the [illegible] and inject venom. They are nocturnal in their habits [illegible] during daylight. Especially the larger species, produce by their [illegible] lesions with accompanying grave symptoms.

The more venomous scorpions produce an immediate, [illegible] pain, burning sensations radiating from the site of the sting [illegible] and systemic symptoms resembling those following the [illegible] The prognosis is generally good, except in young children.

Tight ligature, disinfection of the wound, [illegible] of anti-scorpion serum should be done.



630 Androctonus australis



Scolopendra spec.

## C. CHILOPODA (centipedes)

They are long, slender animals consisting of many segments, each of which carries one pair of legs. Each of the first pair of legs is provided with a claw which serves as a fang, from which the venom flows when the animal stings. They are not equally dangerous; the larger forms (species of Scolopendra, Lithobius, and Geophilus, which reach a length of up to 10 inches or even more) may cause serious symptoms by their [illegible] and even prove fatal in young children.

Erythema, painful oedema and papule formation have been observed

but the sting of most species produces no more than a temporary sharp pain, unless secondary infection develops at the site.

## D OTHER ANIMALS

### 1 Coelenterata (jellyfish and polyps, corals and sea anemones).

Different species of jellyfish (medusae) contain in their ectoderm numerous nematocysts, each with a cnidocil or trigger hair. When persons bathing in tropical seas touch these cnidocils, a thread, at the base of which are minute poisonous barbs, is ejected from the cnidoblasts into their skin. The sting produces an urticaria resembling exanthema, and painful local swelling, often coupled with fever and vomiting lasting 2 days. The stings of tropical species (*e.g. Physalia* and many other genera) are more severe, and in susceptible individuals, give rise to shock and collapse. Recent experiences from North Queensland, where several deaths have already been reported, point to the rôle which a certain species of jellyfish may play. In this case probably *Chiropsalmus quadrigatus* (Scyphomedusae), the "Portuguese man-o war" was the species involved.

Coral dermatitis results from cuts in the skin through contact with the anthozoa; sponge fisher's dermatitis from contact with sea anemones.

### 2. Mollusca (shellfish)

In the Pacific Islands cases of poisoning may be due to certain shellfish of the genus Conus, notably *C. aulicus*, *C. marmoreus*, *C. tulipa*, *C. textile* and *C. geographus*. Several fatal cases have been recorded in the Western Pacific from stings by the two last.

Persons, not thinking of any risk, pick up these handsome molluscs and are poisoned by a potent venom produced by a poison gland and injected through a spinous radicular tooth.

### 3. Hirudinea (leeches)

They are worm-like animals with anterior and posterior suckers; at the centre of the anterior sucker is the mouth, which may be provided with cutting teeth. When living as ectoparasites on man, and in sucking blood, leeches secrete an anticoagulant, hirudin. After gorging themselves they drop off the host. The lesions bleed for some time, heal slowly and may therefore become infected.

Land leeches, which are very troublesome in many tropical regions, climb up man's legs from the ground; aquatic leeches affix themselves to bathers.

Therapy. Application of strong solutions of tobacco juice, to the leeches, or touching them with a lighted cigarette. Oozing of blood should be controlled with a styptic pencil. Guard against secondary infection.

Prophylaxis. Smear shoes and puttees with soap, and keep them moist. Dimethyl phthalate is efficient.

4 **Pisces** (fishes)

Poisonous fishes, which live especially among the coral reefs of the Pacific and Indian Oceans, may convey their venom to man either through their bite (species of Muraena), or by the sting of either dorsal (Synanceia and Plotosus) or pectoral (Plotosus) fin rays by a spine on the tail of the sting ray or by numerous spines on the integument (Scorpaena). These spines are often associated with poison glands, but frequently a coating of mucus is the chief agent responsible for the toxic effect of the sting

The barbed spine of the sting ray can inflict a wound that is painful and dangerous out of all proportion to its size and depth. The narrow grooves which run along the edges of the spine contain a fine glandular tissue which secretes a virulent poison. Penetration of the sharp spine is easy but its edge is serrated and the barbs are directed backwards so that withdrawal leads to laceration of the tissues which fosters absorption and distribution of the poison. In man, the poison produces an immediate, agonizing pain, followed by a considerable degree of cytolysis in the immediate vicinity of the wound. This may necessitate amputation, and may even be fatal (LE MARE).

Other species cause an immediate painful reaction at the site of the puncture, rapidly followed by marked erythema. Systemic effects may supervene death has occurred. The part surrounding the puncture site may become gangrenous.

5 **Ophidia** (snakes)

We shall not here discuss at length the bite of poisonous snakes, since the dermal phenomena caused by it are relatively unimportant.

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CHAPTER 41

# INSECT REPELLENTS AND TOXICANTS

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"The Lord in his wisdom made the fly and then forgot to tell us why."
OGDEN NASH

One of the most significant advances in modern medicine has been the modern developments in the chemical control of insects. This research was of necessity produced by the military requirements of the last war. Research has continued but not on as great a scale. As yet, the goal of the ideal repellent or the ideal toxicant has not been reached. It has been said that many good modern toxicants are not selective in that they destroy the good as well as bad arthropods and in time with prolonged use may disturb the various "biological control" measures which nature has evolved over a period of time. It has not been possible to combine both good repellent qualities and good toxicant qualities in the same compound or even same general mixture.

## EFFECT ON THE ARTHROPOD

The purpose of the repellent is to protect a surface area from actual contact with the arthropod. The exact mechanism of repellency is not understood. Such features as odour production and physical character of the surface may serve as repellent qualities. The purpose of the toxicant is to kill the insect following direct contact or following ingestion as a so-called stomach poison or as a fumigant through the breathing tubes or gas through the skin.

## DEVELOPMENT OF NEW MATERIALS

Many new compounds continue to be developed in this eternal struggle between insects which were in this world first, and man. These materials may either be developed by a study of materials in plants known to be toxic to insects or by routine testings of chemicals of known structure. This latter technique involves the screening usually of thousands of compounds against particular arthropods. The physician must concern himself with the fact that first and foremost all these materials, especially the toxicants, are also toxic to humans. No new compounds should be allowed to be used until detailed toxicological studies have been made. It should not be inferred that the toxicity of a mixture for man can be estimated by a summation of the toxicities of the individual components but it is necessary to repeat the detailed toxicological studies with the mixture as a whole. When these chemical materials are made available to the consumer the directions for consumer usage must be followed thoroughly As a general rule the repellents now in use are materials of low sensitization index. The factor of sensitization must be considered for individual use.

## SOME FACTORS INFLUENCING BITING

One must understand also something about the arthropods to be protected against, their techniques of feeding and something of their ecology before one can understand or attempt to develop a good scheme of chemical protection. Here the physician must work with the entomologist. Some of the factors which may influence an arthropod biting the skin of man for example include such features as the hunger of the arthropod, the moisture of the surface of the skin, the carbon dioxide concentration about the skin surface, the odour light, whether the arthropod gathers singly or in groups the type and colour of clothing and whether or not repellents have been used In addition, there are unknown factors of attraction which seem to make some individuals bitten more easily than others. Sometimes this assumption is only relative because in our experiments with relatively non sensitive reactors under the skin microscope we have observed adequate puncture and feeding by the arthropod with the individual asserting that he has not been bitten.

## AREA CONTROL

Except for some few arthropods affecting the skin of man such as pediculus humanus, phthirus pubis and sarcoptes scabiei, the physician must consider area control as well as personal protection. Area control includes such sanitary environmental measures as cleanliness, absence of water pools, dampness, decaying vegetation, animal hosts etc. In addition, it may be necessary as for example with mosquitoes flies and even chiggers, to have considerable area control techniques by chemical control mechanisms such as sprays and the like. In this field also one must consider toxicity to both humans and animals.

## INDIVIDUAL PROTECTION BY REPELLENTS

To outline briefly some of the practical measures of control as regards repellents we can say that individual protection may take two forms 1 the local applications of various types of medications and 2. the impregnation of clothing with repellent materials. Some of the general considerations of a repellent which are of interest to the physician are the necessity for 1 a wide range of repellency 2. that materials be non-toxic and 3 have only a low sensitivity index. Also these materials are apt to be used more efficiently if they are not bad smelling, irritating to the clothing or to the furnishings. Many good repellents are also solvents and cause changes on varnished or lacquered surfaces or on plastics Many of them also irritate the eyes. To a certain extent the following are the preferred groups of repellents that are for general use

| | Rx 1 | Rx 2 | Rx 3 |
|---|---|---|---|
| A. Dimethyl phthalate | A—3 parts | A—1 part | A—3 parts |
| B Dimethyl carbate | D—1 part | C—1 part | C—1 part |
| C Indalone | C—1 part | D—1 part | B—1 part |
| D Rutgers 612 (2, ethyl -1 3-hexanediol) | Formulae (by wgt.) of U.S Dept. of Agriculture Agricultural Research Administration, Bureau of Entomology and Plant Quarantine. | | |

Duration of repellency—varies up to 2 3 hours.

Repellents are rubbed freely on all exposed areas, for example on wrists arms, ankles, neck and face, with caution to the use about the eyes.

Efforts should continue to be made to attempt also to develop repellent creams Some creams, which have good repellent quality are too thick or too messy to use. No cream should contain perfumed material which might serve as attractors for the arthropods No cream should be used that has not been tested under both controlled laboratory and field conditions for repellency qualities Studies are under way at present to attempt to develop repellent creams which may serve also for protection against sun Indalone, for example, is reported to have a mild sun screening effect.

For certain arthropods a special repellency group of chemicals must be considered. These include for example the tick repellents—N-butyl acetanilide, undecylenic acid, etc. (none completely protective) and for the control of chiggers, benzyl benzoate, diphenyl carbonate and benzil. The first material may be used in the form of cream or lotion. The other two may be used as dust or by impregnating the clothing

One effective way of protection of large body surfaces is the use of impregnating materials with a repellent material. One example of an all-purpose clothing repellent is the mixture

N-butylacetanilide—30 per cent.
Benzyl benzoate—30 per cent.
2-butyl-2-ethyl-1,3-propanediol—30 per cent
Tween 80

This is used diluted one to two parts of water and is especially effective for protection against mosquitoes, ticks fleas and chiggers It is especially valuable in military medicine with uniform impregnation.

Something should be said about the use and perhaps also the abuse of so-called oral repellents It is the feeling of the experienced workers in this field that in spite of the popularity of oral repellents in certain sections of the world, as yet oral repellents have no real protective value. From animal experiences such protection is indeed possible but the developments are not advanced as yet for use in the protection of man. Studies still continue in this field

## A CLASSIFICATION OF SOME TOXICANTS

In the field of toxicants it is emphasized again that from the very nature of the "beast" the toxicological factors for man must be

considered in detail. An example of this is the current interest in the highly effective organic phosphorus toxicants. A practical classification of the toxicants currently available may be considered as follows:

1. DDT—2,2-*bis*(*p*-chlorophenyl)-1,1,1-trichloroethane
2. DDD—2,2-*bis*(*p*-chlorophenyl)-1,1-dichloroethane, TDE, rhothane D-3
3. Methoxychlor—2,2-*bis*(*p*-methoxyphenyl)-1,1,1-trichloroethane, probably safer than DDT about house and dairy barns
4. Benzene hexachloride—1,2,3,4,5,6-hexachlorocyclohexane, GBH, 666, gammexane. Lindane—gamma isomer
5. Aldrin—1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4,5,8-dimethanonaphthalene
6. Toxaphene—chlorinated camphene, a mixture of several isomers, 3956, Hercules 3956
7. Chlordane—1,2,4,5,6,7,8,8-octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindane, 1068
8. Piperonyl derivatives—piperonyl cyclonene, piperonyl butoxide
9. MYL powder (Bushland)—pyrethrum, N-*iso*butyl undecylenamide, *iso*propyl cresols, 2,4-dinitro anisole and pyrophyllite
10. Pyrethrins
11. Parathion—O,O-diethyl-O-*p*-nitrophenyl thiophosphate, 3422, E-605
12. TEPP—tetraethyl pyrophosphate
13. HETP—hexaethyl tetraphosphate
14. Phenyl cellosolve—ethylene glycol monophenyl ether
15. Eurax—crotonyl N-ethyl *o*-toluidide
16. Diphenyl carbonate
17. X,x'-dichloro-diphenyl ether
18. Octamethyl pyrophosphoramide
19. Thiocyanates—lethane 384 (1-thiocyano-3,6-dioxadecane or β-butoxy-β'-thiocyano diethyl ether), lethane 384 special (a mixture of lethane 384 and 2-thiocyanoethyl ester of $C_{10}$ to C acids), lethane 60 (2-thiocyanoethyl laurate)
20. Pyrolan—1-phenyl-3-methylpyrazolyl-(5) dimethylcarbamate
21. EPN—ethyl *p*-nitrophenyl thionobenzene phosphonate (toxic to man and warm-blooded animals)
22. Allethrin—synthetic pyrethrins

This list will be modified from time to time as new chemicals are constantly being developed.

For the physician in the tropics the toxicants for area control include especially DDT, methoxychlor, lindane and chlordane. One must determine whether these be used as sprays, aerosols, dusts or even incorporated into paints, etc.

The actual toxicants for some arthropods of dermatologic interest include

Sarcoptes scabiei—Crotonyl N-ethyl o-toluide (Eurax)
Gamma isomer benzene hexachloride (Kwell)
Cimex lectularius—area control and personal protection
Eutrombicula alfredugesi—area control and personal protection
Pediculus humanus—DDT powder Kwell Eurax lotion
Phthirus pubis—Kwell lotion Eurax lotion
Tick (Amblyomma americanum)—area control and personal protection
Xenopsylla cheopsis—Ctenocephalides canis and felis—area control and personal protection
Liponyssus bacoti—area control and personal protection

Even for the most studied toxicants, DDT and its derivatives, detailed studies of chemical toxicity are still not entirely complete. Features of food contamination through direct application and contamination in the barns and dairy products still have to be worked out. Although there is not a detailed toxicological study on some of the materials available for toxicant action on arthropods in man, for example DDT and benzene hexachloride and Eurax, to mention only a few more popular ones yet the proper application of these materials does not give rise to serious difficulties. One must learn the technique of application as it applies to personal protection as for example arthropods of medical interest, or as it applies to usage in control of arthropods in agriculture Within the brief limits of this article, the details regarding each toxicant cannot be completely evaluated.

For the development of a new chemical material, the following brief stages should be considered

1 Chemical synthesis
2. Study of the toxicology as referable to the arthropod
3 Detailed studies of animal toxicity
4 Screening tests and usage tests for cutaneous irritation and sensitization
5 Detailed toxicology studies in man following various types of applications and including clothing impregnation
6 Studies of limited carefully controlled consumer use and abuse

## CONCLUSION

It is important that the physician understand the background in the

development of the chemical measures, repellent and toxicant, against the arthropod. Those who have need of continued use of these must keep abreast with the rapid developments in this field.

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# SPARGANOSIS

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## DEFINITION

Sparganosis is a disease due to larval forms called *Sparganum* of various species of the tapeworm *Diphyllobothrium* (*Cestoda*) They are flat worms measuring 8 to 36 cm long, 1 to 2 mm wide The scolex is similar to that of the adult and bears two sulci.

In the life cycle of the genus *Diphyllobothrium* *Sparganum* represents the plerocercoid, that is the larva issued from the procercoid larva which is formed in the intermediate host *Cyclops* (*Copepoda*)

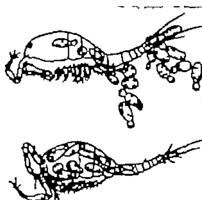
## AETIOLOGY AND PATHOGENESIS

It is known that in the case of the human tapeworm, *D latum* Sparganum lives in the peritoneum or in various organs and muscles of various fishes. If the fish is eaten by man who is the specific host for that species the adult worm develops in the intestine. If the fish is swallowed by another fish a special phenomenon takes place. It was described by FUHRMANN and BAER for the human tapeworm and OKUMURA for *D mansoni* The Sparganum passes through the gastric wall and re-encapsulates in this new host, and so on till it is absorbed by man, where it develops into an adult worm.

In the case of human sparganosis man is a non specific host in which re-encapsulation of the plerocercoid takes place for the larva belongs to an adult *Diphyllobothrium* living in dogs and cats This

Sparganum may be found in many vertebrates except fish. Man be comes an intermediary host.

Much confusion has been created in the determination of the species involved in the process. Spargana are all identical and it is necessary to feed them to dogs or cats to obtain adult tape worms.



631 Procercoid larvae in Cyclops.

## CLASSIFICATION

BRUMPT admits 1 *Diphyllobothrium mansoni* COBBOLD Adult in dogs and cats. Sparganum in man and numerous vertebrates (batracians, reptiles) except fish Rats, mice, guinea-pigs, all mammals are susceptible.

2. *D erinacei europaei* RUDOLPHI (1819) (*D ranarum D reptans*) adult different from the preceding Found in dogs and cats in Europe and Asia. Sparganum in batrachians, reptiles and mammals.

3 *D decipiens Diesing* 1950 CHANDLER (1925). Adult in cats (America and Asia).

4 *D mansonoides* MUELLER 1935 Adult in dogs, cats, and some species of wild fox in the United States. Sparganum obtained in mice, rats, leopard frog, some monkeys and, experimentally in man.

Sparganosis is conveyed to man by absorption of water with cyclops containing procercoid larvae or of plerocercoid larvae, or Sparganum, from susceptible vertebrates.

In 1912 VON RATZ fed Sparganum of *D raillieti* on dogs and obtained an adult. YAMATA YOSHIDA, OKUMURA, EVANNO for *S mansoni* obtained the same results OKUMURA demonstrated re-encapsulation. The scolex of Sparganum separates from the body and pierces alone the wall of the stomach.

OKUMURA demonstrated that the life cycle was similar to that of *D latum* (ROSEN and JANICK) From the egg escapes a ciliate larva (coracidium) which grows in Cyclops and becomes procercoid. If cyclops are swallowed by various vertebrates except frogs and cats procercoids pass through the digestive wall and transform into plerocercoid or Sparganum in the organism. Man gets infected by the same process, or by eating flesh of vertebrates containing plerocercoids which re-encapsulate in his organism.

BONNE in Java, GALLIARD and NGU in Tonking showed that tadpoles were extremely susceptible to procercoid contained in Cyclops, whilst frogs were refractory nevertheless these latter authors never succeeded in finding naturally infected tadpoles which therefore seem to have no importance in epidemiology

**SPARGANOSIS IN MAN**

MANSON found the first human case in a Chinese at Amoy The disease seems rather common in Japan. YOSHIDA showed that Sparganum from man fed to cats produce the same adult worm as when Sparganum come from frogs in which they are very common. KOBAYASHI in Korea observed only three cases in man, though frogs are never in fected. Adult worms are found in dogs wolves foxes, leopards tigers EVANNO in Annam, HOUDEMER at Hanoi obtained worms in dogs by feeding them with Sparganum from man.

**SYMPTOMATOLOGY**

Sparganosis is generally symptomless unless larvae occur under the skin. MANSON found larvae in the sub-peritoneal connective tissue, once in the pleural cavity

IJAMA and MURATA report 7 cases in three, larvae were expelled from the urethra, in 3 others they were found in the eye in the subconjunctival tissue One case was remarkable the parasite was in the subcutaneous tissue. During nine years a painless tumour appeared at the same place on the thigh, each summer At last an abscess was formed and the larva was expelled.

BONNE observed at the post mortem examination of a Malayan a large haemorrhagic infarctus of the right lung some smaller in the kidneys and brain, a local fibrinous peritonitis round the ascending colon In

the arteries of the infarcted lung the author found pieces belonging to one specimen of Sparganum, probably *S. mansoni*. The author explained the abnormal localization in the lung by the presence of persistant *foramen ovale* in the patient's heart.

MUELLER and GELDSTEIN demonstrated that cases of Sparganosis, in the United States, were due to *D. mansonoides* by placing under their own skin young larvae which reached 30 times their original length 3 months later.

In Belgian Congo FAIN removed a Sparganum, 1 meter long, coiled in the connective tissue surrounding the spermatic chord just above its entrance into the scrotal sac. In the same area the author found



632. Sparganum above and around the eye in tadpoles.

adult Diphyllobothrium in chacals (Thos adustus) and servals (Felis serval).

A case of "cystic" sparganosis of the lumbar region was reported in a patient coming from Gaboon (HARANT and COLLAB). The tumour was painful, and pain seemed to have taken place five years prior to the appearance of the tumour. A typical larva of 4 cm was removed from the cyst.

## OCULAR SPARGANOSIS

Plerocercoid larvae may in some circumstances produce very severe ocular lesions. This clinical aspect occurs rather commonly in Tonking and some parts of China. It is not due to larva migrating from the digestive tract but to empirical methods of traditional practitioners. Skin or flesh of frogs are put on the eyes as sort of plaster and Sparganum migrate directly into the periocular tissue. Since 1911 the attention of French medical officers has been drawn to this

peculiar disease. (PAUCOT COLLIN CAZAUX, MOTAIS, EVANGO HOUDEMER) IJIMA and MURATA in Japan, where cases are much rarer believe that larvae may proceed to the eye by migration. GALLIARD and NGU (1930) noticed that in infection of tadpoles conveyed by infected Cyclops the Sparganum are localized most frequently around or above the eye.

Larvae may be sub-conjunctival, palpebral, retrobulbar They are often found under the skin of the temporal or frontal regions. The lesions are only painful in case of secondary bacterial infection. The symptoms are palpebral oedema, ocular occlusion. When the larva is retrobulbar exophthalmia, even subluxation of the globe may take place. Symptoms are most severe and are complicated by ulcer of the cornea, papillary congestion, haemorrhagic retinitis and panophthalmia

The prognosis of ocular Sparganosis is not severe if the eye was previously normal But when forementioned treatment of ocular troubles (conjunctivitis,



633 Spargan m piercing the gastric wall of the frog

trachoma, ulcer of the cornea) is applied, complications often occur

Surgical treatment is easy in some cases Injections of alcohol, of oxycyanide of mercury in the site of the parasites neoarsphenamine intravenously have given satisfactory results.

*Sparganum prolifer* In Japan IJIMA (1905) discovered in small cysts of 1 to 8 mm long worms resembling Sparganum, though the head was deprived of bothridia. These larvae may multiply by transversal scission. New heads may be formed Lateral proliferating processes may separate and develop independently YOKOGAWA (1933) failed to infect animals by ingestion the larvae are digested. Nevertheless TOSHIRO observed that transplantation of larvae from man under the skin or intra peritoneally in monkey dog and guinea pig produced

an intense proliferation. The exact nature of this Sparganum is not yet defined.

Sparganum prolifer is vastly distributed (Japan, Texas) but cases are very rare. It is found in cysts which are sometimes very numerous under the skin. The lesions are very noticeable. The patient of IJIMA showed a swollen thigh, with an acneform eruption A patient of TOSHIRO, aged 25 when she died had the whole body covered with subcutaneous nodules and abscesses from which living worms were expelled. An immense quantity of larvae were recovered from the subcutaneous tissue, muscular fasciae, wall of the intestine, mesentery kidneys, lungs heart and brain.



634 Sparganum in the gastric wall of the frog

## DIAGNOSIS

Diagnosis of this disease seems very difficult. The cases are very rare, sporadic, and parasitism is only obvious when larvae are visible under the skin where palpation may reveal the presence of nodules. In some cases the region is swollen, abscesses are formed and the larvae are expelled.

Sparganum prolifer seems to be the most pathogenic and besides swelling or tumour and abscesses, may cause cutaneous eruptions

Ocular sparganosis is easy to diagnose and the patient speaks about the special treatment with flesh or skin of frogs or serpents, which was given him by a quack.

## THERAPY

No treatment exists other than extirpation of the superficial nodules Treatment may be applied to secondary infection when it occurs in the case of abscesses.

As we have said ocular sparganosis must be treated surgically in some cases of exophthalmia, or locally by injection of alcohol, or intravenously with arsenobenzol.

## PROPHYLAXIS

The cases are so rare, so patchy that it seems useless to recommend general measures to avoid infection. But in countries like Tonking where ocular sparganosis is common, prosecution of illegal practitioners propaganda by teaching in schools, cinema, posters seemed to be effective.

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# SCHISTOSOMAL AFFECTIONS OF THE SKIN

## (Swimmer's Itch)

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Skin lesions due to the cercariae or ova of the many different schistosomes may be conveniently divided into three types

1. *Cercarial dermatitis* usually produced by the cercariae of the non human schistosomes especially those of birds.
2. Skin lesions of an anaphylactoid character appearing in the *Katayama stage* of bilharziasis four to six weeks after the original infection by the cercariae of human schistosomes reaching maturity in the liver (The Early Toxic Stage)
3. *A dermatitis in the later stages of the disease* caused by embolic ova which provoke an inflammatory and fibrotic reaction.

### CERCARIAL DERMATITIS (SCHISTOSOME DERMATITIS, SWIMMER'S ITCH)

This dermatitis is due to the penetration of the skin of man by certain schistosome cercariae of birds and mammals It has a world wide distribution, but is best known in the United States of America and Canada In the United States it is endemic in the north central lake region, especially around Wisconsin and Michigan. BUCKLEY (1938) has recognized it in Asia in the Federated Malay States where it is known as "Sawah itch" and caused by the cercariae of the cattle schistosome S *spindale* Kabure itch" in Japan, originally considered due to cercarial penetration by S *Japonicum* is now believed by some workers to be produced by a non human schistosome. From Lake

Rangoon in Burma and Mysore in India, as well as from New South Wales in Australia and from New Zealand, the disease is recorded It is reported too from Africa where it is caused mainly by *S bovis* (RAPER, 1951)

BARLOW (1936) in Egypt produced the itch and rash experimentally in man exposed to the cercariae of *S haematobium* and *S mansoni* and showed that under certain conditions the dermatitis could be introduced in farm labourers working for long periods in canal water, in which the snails were infected with the human schistosome. This, however from all accounts, appears to be uncommon.

It is not without interest that cercarial dermatitis is also described in bathers using a small artificial lake near Cardiff Wales, and that on the Continent of Europe it is encountered in France and Switzerland.

*C stagnicola* is the most important dermatitis-producing cercaria in the United States of America and Canada, being responsible for most of the "swimmer s itch" there. *C elvae C physellae* and occasionally *S douthitti* are less significant but cause some of the infections. In New Zealand *C longicauda* in Malaya *S spindale* in Japan *C sturniae* and in Europe probably *C ocellata* are considered the producers of this skin eruption.

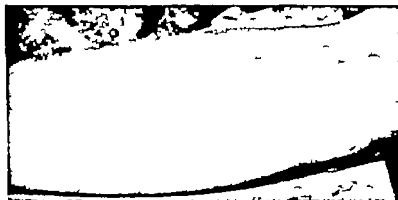
The intermediate host of *C stagnicola* which causes most of the dermatitis on the bathing beaches of the United States of America is *S emarginata*. The snails are heavily infected in the summer, during which season the cercariae are given off, the first cases being reported in late June or early July The peak of cercarial production is reached during July as the hot weather speeds their development. This coincides with the height of the swimming season, the bathers also being attracted to the water by the heat. Thus the majority of cases of "swimmer's itch" are to be expected at that time of the year

The cercariae of *C stagnicolae* and *C elvae* mostly escape from the snails in the early morning and those of *C douthitti* in the early evening They are attracted to light (positively phototactic) and are mainly found close to the surface of the water, which they reach by their own movements or are carried along by the surface currents. They are very sensitive to passing shadows which cause them to swim around vigorously

It usually takes several minutes from the first application of infected

water before the bather feels the prickling sensation. It is generally held that water containing the cercariae must evaporate on the skin before they can penetrate through a cleft or wrinkle into it. An area which is rubbed immediately shows fewer lesions. Experiments however demonstrate that the cercariae can enter the skin whilst the bather is fully emerged, thus not requiring an evaporating film of water to stimulate their entrance.

Little is known of the definitive hosts in which the cercariae reach maturity. Two species develop in mammals and the rest in birds. Various cattle and other herbivora serve as definitive hosts for *S. spindale* whilst those of *S. douthitti* are wild mice and musk rats. One



635 Papular eruption after exposure of forearm to the cercariae of S. mattheei. Photograph taken 22 hours after contact.

*(Alves–Salisbury, S. Rhodesia)*

type of cercaria favours blackbirds, another starlings and sparrows, but the natural hosts of most of the other species are ducks, mainly wild ones.

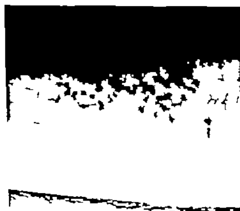
## SYMPTOMATOLOGY

The reaction to penetration of the skin by the cercariae of the schistosomes of man is usually mild. Often no lesions are produced, merely a prickling sensation being mentioned.

The reaction resulting from the entry of the cercariae of the non-human schistosomes, however, is often severe. In a typical case a

prickling or itching sensation follows penetration of the cercariae. This continues for about an hour when small macules about 1 mm in diameter appear at the sites of entrance. The macules persist for several hours and are replaced by discrete papules, 3–5 mm in diameter. This change is accompanied by severe itching. Instead of the macular reaction a diffuse erythema or a local urticaria may be produced. By the second or third day vesicles form in the papules and may occasionally form pustules from secondary infection. The lesions may become confluent, and the whole area swollen and oedematous. After about a week the papules disappear leaving small pigmented spots on the skin.

It would appear that the sensitivity of each individual varies and that the body becomes increasingly allergic to the protein of the cercariae with repeated infections. Whereas the typical reaction to the first exposure is generally an initial sharp bout of itching of short duration with the formation of macules and papules, after repeated infections it is liable to be severe with larger and redder lesions which often become vesicular.



636 Collector's or Swimmer's itch. Schistosome-dermatitis.
*(Orr G Carle-Bele Herrgeate)*

**THERAPY**

As the rash clears spontaneously there is little cause for anxiety except to warn the patient against scratching and thereby introducing secondary infection. This is best avoided by the application of phenolized calamine lotion. Anti-histamines may be worth trying.

### PROPHYLAXIS

The prevention of snail infection is extremely difficult, as one cannot control the migration of birds. For the destruction of the snail, copper sulphate in high dilution has been used with success in small artificial lakes, but has not been effective in vast stretches of water. Protection of the bather's skin by a protective oil or grease has not proved popular. Collectors and others who have to enter the water should wear hip boots and other protective clothing. A simple but useful measure is the vigorous rubbing dry of the skin immediately on leaving the water. This greatly reduces the risk of penetration.

### THE EARLY TOXIC STAGE OCCURRING FOUR TO TEN WEEKS AFTER INFECTION BY THE HUMAN SCHISTOSOMES ASSOCIATED WITH TOXIC AND ANAPHYLACTIC FEATURES

*Katayama* or the allergic stage of bilharziasis is the reaction to the presence of the cercariae and their development into adulthood within the body, particularly in the liver. The illness may follow infestation by any of the three human schistosomes, but probably more commonly with *S. Japonicum* and *S. mansoni* than with *S. haematobium*.

In China the condition is known as *Yangste River fever* and in Japan as *Katayama*. It usually commences about six weeks after exposure, and its chief features are fever (which may be prolonged, thus resembling typhoid and abortus fevers), urticaria, joint pains, bronchitis, enlargement of the liver and spleen and diarrhoea. A high eosinophilia is always present in the blood. The syndrome varies in intensity from mild to severe. In some cases the chief manifestation may be the red urticarial swellings indistinguishable from food poisoning. The symptoms generally clear up after a few weeks, only to be followed sooner or later by the excretion of viable ova in the stool or urine, and by other signs of bilharziasis.

### THERAPY

Treatment with one of the trivalent salts of antimony, preferably sodium antimony tartrate, will effect a cure at this early stage.

### LATE CUTANEOUS BILHARZIASIS

In the later stages of human bilharziasis, the ova, probably embolic in nature, are occasionally deposited in ectopic sites, such as the skin,

forming a papular or nodular eruption, which, in severe cases leads to papillomatous or warty growths. In my experience, vulval warty masses, encountered in regions in which bilharziasis is endemic, are not uncommonly due to this disease. The diagnosis can be established readily by submitting a portion of the growth for histological examination.

## THERAPY

Treatment consists in the administration of one of the antimonial preparations and, if necessary, surgical removal of the swelling, provided it is in an accessible place.

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CHAPTER 44

# ONCHOCERCIASIS

## (Volvulosis)

F PIERS – Nairobi

PAUL FASAL – San Francisco

### DEFINITION

Onchocerciasis is a filarial infection characterized by the presence of numerous microfilariae in the cutis, the formation of subcutaneous nodules certain cutaneous eruptions and eye lesions, which can lead to blindness caused by the nematode Onchocerca volvulus Some authors distinguish *Onchocerca volvulus* (Africa) from *Onchocerca caecutiens* (Central America) The two organisms are morphologically identical. Clinically the disease presents somewhat different aspects in the two continents

### EPIDEMIOLOGY

Infection with Onchocerca volvulus occurs through a wide belt of Tropical Africa, from the Guinea Coast through the Congo Basin to Uganda, the Lake Province of Kenya and the Southern Sudan. The distribution resembles that of Loa loa, but exceeds the endemic areas of that disease considerably The chief sufferers are natives living in river valleys with dense tropical vegetation Europeans are rarely affected In America the disease is found on the Pacific slopes of the Central American Plateau in Guatemala and the adjacent districts of Mexico (Chiapas, Oaxaca) at an elevation of between 330 and 1500 m above sea level the coffee planting people are heavily affected. In Central America the spread of the disease is slowly northward.

**AETIOLOGY**

Unlike the parasites described in following chapters Onchocerca volvulus is exclusively a parasite of the connective tissue of man in all its stages of development. The microfilariae are abundant in the corium, while the adults are found in fibrous nodules, which will be described later Only on exceptional occasions have microfilariae been seen in the blood.

The male adult worm measures from 18 to 45 mm in length and 100 to 200 micra in thickness the corresponding measurements of the adult female are 35 to 50 cm in length and a diameter of 200 to 500 micra. The larvae (microfilariae) are 150 to 360 micra long and 5 to 9 micra in diameter The cuticle of the adult is striated both ends are



637 Onchocercomata of the scalp.
*(Jadassohn's Handb für Haut Geschl Kr.)*

tapering, the tail is sharply pointed. Nuclei are present almost to the tip of the tail.

The life history of Onchocerca resembles that of other filariae in so far as the worm depends on an insect for its development and transmission. The vectors of Onchocerca volvulus are flies of the genus *Simulium*—very small black gnats with a well developed thorax which gives them a humpback appearance—hence the popular name "*buffalo flies*" while in Guatemala they are known under the name of "*coffee flies*" they breed in running, well shaded water, and sting in the

daytime only The species known to carry Onchocerca volvulus are *Simulium damnosum* and *S neavei* in Africa in America the species in question are *Simulium ochraceum S pallidum (mooseri)* and *S metallicum (avidum)* All simulia are voracious feeders and may inflict extremely painful stings. Infestation with Simulium may render entire districts uninhabitable The saliva injected by the fly attracts the microfilariae which are then sucked in with the blood. The ingested larvae undergo development in the thoracic muscles of the insect for 7–10 days and

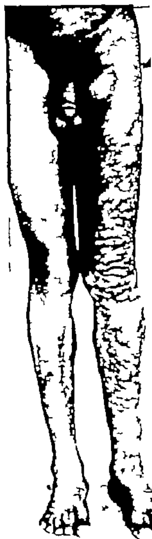


638 Onchocercoma behind the ear

then migrate to the mouth they are transmitted to a human host when the insect bites again, and penetrate actively through the skin

It takes at least two generally ten months from the infective insect bite to the formation of the nodule called onchocercoma which contains one or more adult worms Five months are required for the fecundation of the female worm inside the nodule The microfilariae produced in the onchocercoma live approximately for eight months

in the skin. *The formation of nodules is not an invariable feature of the disease* in the infrequent cases of onchocerciasis of the African type in Europeans nodules have rarely been seen. This observation does not hold



639 Chronic onchodermatitis in a 15 year old boy with microfilariae in the skin lesions. Note femoral bubo.

*(Jelliffe–Ibadan)*

true for the American type, where onchocercomata have occurred in Europeans.

The most impressive feature of onchocerciasis is the presence of enormous numbers of microfilariae in the corium, frequently in areas where the skin appears normal on inspection. They can easily be demonstrated in histological sections or by the methods which will be described later

## SYMPTOMATOLOGY

Intensive *pruritus* is the most prominent subjective symptom in the African type. As in all cutaneous affections with prolonged itching the skin may become lichenified. This is however not an invariable



640 Sectioned nodules of volvulosis.

feature in several cases of African onchocerciasis seen in Europeans by one of the writers (F P) there was no trace of lichenification, although the infection dated back many years and itching was most violent. *Sclerodermitis* as in Prurigo Hebrae often accompanies lichenification Excoriations are infrequent. A "*xerodermatous*" condition of the skin—resembling ichthyosis— has been described as a symptom of onchocerciasis It may be that the presence of millions of filarial larvae in the lymphatic spaces of the cutis interferes to some extent with the metabolism of the skin, and so produces a dry rough and scaly skin, but there is no conclusive proof for this theory It should be noted that microfilariae produce very little reactive inflammation and hardly any vascular response in the corium On the other hand "xerodermatous" and pseudo-ichthyotic skin changes are frequently seen in natives of tropical countries they often accompany chronic mal

nutrition or infections of all sorts. In patients suffering from onchocerciasis the dry scaly skin may be due to coincidence of helminthic infection with other factors. *At present one can not claim "xerodermatous" skin as a specific symptom of onchocerciasis*

In the American type of the disease, erysipelas-like rashes affecting the face, and accompanied by fever and marked oedema of the skin have been described as "*erysipelas de la costa*" or if there is a more purplish color to the facial eruptions as *mal de morado*" This type of eruption is generally associated with the eye lesions of onchocerciasis



641–642. Giant elephantiasis of the face due to volvulosis in the Belgian Congo. *(Lapierre–Liège)*

It was a case of erysipelas-like eruption of the face in a child with eye trouble and a tumor of the forehead which enabled ROBLES to recognize the disease in Guatemala in 1925 and so diagnose the first case of the American type. The specificity of this type of facial eruption is controversial it has been suggested that it really is a low grade coccal infection, induced by scratching on the other hand disturbances in the blood supply through vasodilatation and lymphoedema, possibly owing to a vascular allergy have been thought to be responsible The distribution about the face and neck corresponds to the frequent involvement of these parts in American onchocerciasis.

*Lichenification* of face and extremities is another manifestation, frequently seen in cases of onchocerciasis of the American type Severe pruritus accompanies the cutaneous lesions. Another type of onchodermatitis resembles an eczematoid dermatitis, affecting mostly the extensor surfaces of the extremities.

While the specificity of the described cutaneous manifestations is not established with absolute certainty clinical observations and improvement after removal of the onchocercomata strongly suggest it.

The striking feature of onchocerciasis is the fibrous nodules containing the adult worms *(onchocercomas)* The typical sites of these are



643 Onchocercomata of the scalp and the trunk
*(Dubois van den Berg Dis of the warm climates)*

the lateral aspects of the thorax, and the iliac crests in Africans they also may be found over the greater trochanter of the femur the sacrum and in the neighborhood of large joints where they may resemble the juxta articular nodes of yaws In the American type of onchocerciasis nodules are more limited in their distribution they occur on the head neck and shoulders but are most frequently found on the scalp especially in the occipital region. It will be noted that the nodules prefer sites in which a bone is close to the surface The differences of localization in the African and American types have not yet been sufficiently accounted for one of the explanations that have been advanced is that

the body surface of the African is more exposed to the bites of Simulium than that of the Central American in Guatemala and Mexico but it is doubtful whether the localization of the nodules bears any relation to the original site of infection the insects bite certainly as frequently around the ankles and legs as on the head and trunk.

The nodules range in size from that of a pea to that of a golf ball or even larger in the African type from 2 mm to 5 cm in the American type. The number in the American type is usually between 1 to 5 per person, but occasionally there are more, as many as fifty They are indolent, firm, usually freely movable over the bone, and of a



644 Onchocerciasis microfilariae in the dermis.

tough, non-cystic consistency They may persist indefinitely without undergoing absorption. Suppuration is rare. As mentioned above, they do not represent an invariable feature of the disease.

*Eye lesions* are the most sinister feature of the disease They appear to be more frequent in the American form. Conjunctivitis iridocyclitis, glaucomatous manifestations, punctate keratitis and pannus of the cornea with consecutive blindness have been described. Photophobia, blepharospasm and lacrimation are marked in the early stages. The microfilariae can be demonstrated in the anterior chamber of the

eye with the help of the slit lamp as thin, refractive, constantly moving filaments. In some areas up to 30 per cent of the sufferers from





645–646 Section through the adult worms in sectioned onchocercoma.

onchocerciasis became blind although in other districts this figure amounts only to one per cent.[1]

[1] GOLDMAN has described a triad in tropical America consisting of subcutaneous onchocercomata, onchophthalmia and a non-specific onchodermatitis.

A further—uncommon—complication of African onchocerciasis is elephantiasis of the scrotum in men, and adenolymphocele of the inguinal regions in women. A monstrous, but fortunately unique instance of giant elephantiasis of the face, has been observed by LAPIÈRE in the Belgian Congo Elephantiasis of the lower extremities so common in cases of infection with *F Bancrofti* has so far not been observed in onchocerciasis

The *mortality* of the disease is very low but the possibility of blinding eye complications renders the prognosis for untreated cases unfavourable.

## PATHOLOGY

The onchocercomas show on macroscopic sections a firm white cut surface, with a few areas of softening in the centre. There is no well defined capsule. Histologically the outer zone of the nodule shows a productive type of inflammation, followed by a broad zone of dense fibrous tissue, which forms the greater part of the nodule. In the centre the fibrous tissue is somewhat looser, and numerous adult worms are embedded in it. The uteri of the females contain eggs and larvae in various stages of development. In the areas near the worms one often finds patches of inflammation dying or dead worms act as foreign bodies, and attract plasma cells, eosinophilic leukocytes and giant cells In older nodules the centre is often a structureless gelatinous mass in which the remainders of dead worms are seen in faint outline. Foci of fat necrosis occur in the stroma of the nodule. Microfilariae are frequently found in the lymphatic clefts of the fibrous tissue, and in the neighbourhood of the nodules it is probably through the lymphatics of the nodule that they escape from their birthplace to the skin. GABATHULER reports the interesting fact that in a number of nodules he removed the centre consisted of a solid mass of urea crystals. Whether urea is a metabolic product of adult filariae is unknown these findings have as yet not been confirmed by other observers. After the death of the filariae, hyalinization and calcification take place in the nodules It is doubtful whether the nodules may give rise to malignant growths this would at all events be an extremely rare complication.

The changes in the skin are not specific and in most cases very mild. Microfilariae are seen in the corium and occasionally in the deeper

layers of the epidermis. In the corium they are mostly seen in the upper layers, close to the epidermis, especially in the tips of the papillae. There is no inflammatory reaction around the microfilariae. The blood vessels are dilated and show a perivascular inflammatory infiltrate consisting of lymphocytes histiocytes eosinophilic leukocytes and occasionally plasma cells In onchodermatitis with prevalence of oedema, like in mal de morado the epidermal changes are minute, while there is marked separation of the collagen fibers in the corium and fragmentation. If lichenification prevails the epidermal changes consist of hyperkeratosis and acanthosis with a marked perivascular lymphocytic infiltrate in the corium.



647 Sebaceous cyst which was mistaken for volvulosis
*(S mont Amsterdam)*

### DIAGNOSIS

It is not difficult to demonstrate microfilariae in the skin. They are most numerous in the vicinity of nodules but, since they are practically ubiquitous any suitable site may be selected for a specimen. A small piece of skin is shaved off or snipped off (under local anesthesia in sensitive patients) and put into a watchglass with a few drops of warm saline Teasing the specimen with a pair of entomological needles liberates numerous microfilariae from the corium, which may be seen under the microscope (40 ×) moving about in the fluid centrifuging off the fluid facilitates the diagnosis Nodules may be punctured with a thick bore canule to demonstrate adult filariae as the worms are firmly embedded in the dense stroma of the nodule this method usually produces fragments of worms only

The eosinophilic leukocyte count in onchocerciasis is high (up to 60 per cent) but unfortunately it is difficult to exclude other causes for it. Intracutaneous tests and complement fixation may be employed as in other types of filariasis, but are of more theoretical interest owing to the facility of diagnosis by simpler means also they are not as yet specific enough for practical purposes *Xenodiagnosis can be utilized* also This is a method in which the vector is allowed to bite the individual suspected of the disease, and is then dissected and examined for the organisms.

### THERAPY

Until very recently the only effective therapeutic measure was the excision of all the onchocercomata. Various drugs which were recommended, like antimony arsenicals, mercurials, Bayer 205 etc. did not have any appreciable effect.

*Hetrazan*[1] (1-diethylcarbamyl-4-methylpiperazine hydrochloride) a drug introduced by HEWITT for the treatment of Filariasis bancrofti, is now being used in the treatment of onchocerciasis with most promising results Microfilariae disappear after a few doses of hetrazan have been given. The dosage is 2 mg per kilogram of body weight, three times daily for twenty days. Toxic symptoms are rare. BURCH states that pruritus is a common and probably a pathognomonic feature of hetrazan therapy in onchocerciasis. GARNHAM and MCMAHON were remarkably successful in eliminating simulium flies from a district in Kenya which was so severely infested that it had to be closed to settlement. A solution of 2 parts in one million of DDT was used to destroy the larvae of the fly in the two rivers of the area in which the flies bred The effect was drastic simulia disappeared completely from the district which now has been reopened. An unfortunate by-effect of this measure was the destruction of the fish fauna in the rivers but it is hoped that re-stocking will take place in due course from the upper reaches of the streams.

[1] The British name is BANOCIDE.

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# LOAIASIS

(Loasis)

F PIERS
Nairobi

## DEFINITION

A filarial infection, the chief symptoms of which are 1) the diurnal periodicity of microfilariae in the bloodstream and 2) the appearance of transient cutaneous swellings.

## EPIDEMIOLOGY

The disease is limited to tropical Africa. The centre of infection is in the Cameroons and the country around the mouth of the Ogowe River but the disease occurs in a wide belt of country extending from Sierra Leone along the Guinea Coast through the Congo Basin and as far as the Equatorial Province of the Sudan. Generally the rate of infection is heaviest among the inhabitants of the coast districts and decreases further inland

Africans and Europeans are equally affected.

## PATHOGENESIS

The adult worm, *Filaria loa* lives in the connective tissues of man the microfilariae are found in the circulating blood in daytime, but less constantly and in lesser numbers than those of *W bancrofti*

The measurements of the adult worms are 300 mm length, about 0 4 mm thickness (males) 550 to 700 mm by 0 45 mm (females). They possess a bossed cuticle and a sheath the tail is tapering and nuclei may be seen up to the tip of it. Microfilariae measure 200 by

7 μ. The life history of *F loa* is analogous to that of *W bancrofti* but the insect vectors of *F loa* are flies of the genus *Chrysops* ("*Mango flies*") the two principal species known to transmit loaiasis are *Ch dimidiata* and *Ch silacea* Whether other bloodsucking diptera (genus Haematopota) are capable of transmitting the infection is still an open question.

Chrysops flies bite in daytime only In endemic districts a high percentage of wild Chrysops have been found to be infected with *F loa*

As in other types of filariasis, the microfilariae ingested by the insect undergo development (but no multiplication) in the thoracic muscles



648 Calabar swelling in loaiasis
(*Manson Bahr—London*)

of the fly after having reached the infective stage they migrate towards the oral parts from which they escape into a human host when the insect feeds. Their period of infectivity is limited If the insect has no occasion to suck blood during that critical period the microfilariae die and are absorbed

In the human host the larvae attain maturity during this period they wander through the connective tissues of the host causing general irritation and localized swellings. They appear to be attracted by light and heat and have a specific preference for the region of the eye and the circumorbital and conjunctival tissues After copulation the worms

become sessile and retire to the retroperitoneal connective tissues where they may persist up to 15 years. Swarms of microfilariae are periodically emitted into the bloodstream. The larvae appear in the circulating blood during daytime they are most numerous between 10 a.m. and 2 p.m.

### SYMPTOMATOLOGY

The presence of microfilariae in the blood does not appear to cause much systemic illness—except perhaps for a mild filarial fever"

The migration of the adolescent worms through the connective tissues of the skin and of other sensitive organs (e.g the neck of the



649–650 Microfilaria loa in blood film.
*(Ten Berg–Rotterdam)*

bladder) produces pruritus and local irritation both in moderate degree. The worms have a predilection for the tissues of the eye where their appearance may give rise to considerable pain and reactive in flammation. In some instances cyst like swellings containing adult worms have been found in visceral organs. Multiple infection seems to be frequent up to 30 adult worms have been recovered from one individual on autopsy

To the dermatologist, the so-called Calabar swellings" (Calabar a port in Nigeria) are the most interesting manifestations of loiasis.

These are areas of cutaneous oedema, usually of the size and shape of half a tennisball, or even larger. They may appear single or in groups at any site, mostly on the skin of the extremities or of the face. They are well limited, hot and doughy to touch; the skin appears to be thickened by cutaneous oedema and pits slightly on pressure. Some itching and irritation is complained of. The colour of the swollen areas is more or less that of the surrounding healthy skin. Complete resolution takes place after a few days, but recurrence at the same or other sites, sometimes at fairly regular intervals, is the rule. Suppuration of the swellings has never been observed. The nature of the Calabar



651. Microfilaria perstans, which has sometimes been reported in mixed infection with loiasis. It lives in the mesenterium and perirenal tissue. It is resistant to hetrazan-therapy.

*(Jen Berg–Rotterdam)*

swellings has been the subject of much speculation. Originally it was thought that the appearance of a Calabar swelling marked the emission of a new swarm of larvae from the adult female worm. Another theory connected the appearance of a swelling with death and absorption of an adult worm. The more rational view advanced by N. Hamilton Fairley that the swellings are anaphylactoid reactions of the skin to filarial protein is now generally accepted. The swellings thus are a special form of angioneurotic oedema caused by helminthic protein as an antigen. Urticaria may also occur.

Intracutaneous tests with extracts from related filariae and complement fixation tests with similar antigens have been used to prove the high sensitivity of patients suffering from loiasis to filarial protein.

As in all helminthic infections the eosinophilic count is a measure of the allergic response of the organism. It is singularly high in F. loa infection.

The disease is self limited. The symptoms usually subside after the death of all adult parasites, and if reinfection has been avoided (transfer to Europe or other non-endemic countries). The general prognosis is good as the presence of microfilariae in the blood does not seem to cause any damage to the organism.



652. Unilateral palpebral oedema or ophthalmo-glandular complex in Chagas disease which should not be taken for a Calabar swelling.

*(Alberto E. Mazza Sato-Buenos Aires)*

**DIAGNOSIS**

The disease can be diagnosed by microscopical examination of the blood (thick drop), as in F. bancrofti. Specimens should be taken between 10 a.m. and 2 p.m. The blood count shows leukocytosis and a high eosinophilic count (up to 70 per cent.)

Intracutaneous injections of extracts from Dirofilaria mitis (0.25 ml of 1 1 000 extract) and complement fixation tests with extracts from the same parasite are strongly positive in loaiasis

The appearance of an adult worm under the conjunctiva of the eye is most certain proof of loaiasis

## THERAPY

STEPHANOPOULO SCHNEIDER, MURGATROYD and WOODRUFF SHOOKHOFF DWORK *et al* have reported good results following hetrazan therapy It should be given in three to four courses of ten to twenty days each (one month interval) The daily dosage three times daily 2 milligram per kilogram bodyweight. The value of desensitizing measures—injections with filarial antigen—to reduce the frequency of Calabar swellings is disputed The new antihistaminic drugs (Benadryl Pyribenzamine etc.) certainly deserve a trial in this condition Adult worms can be removed under local anaesthesia when they appear in the conjunctiva as the infection is usually multiple this rarely effects more than a partial cure.

## PROPHYLAXIS

General anti fly measures

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# CHAPTER 66

## DRACONTIASIS

### (Guinea or Medina worm)

F PIERS
Nairobi

#### DEFINITION

Dracontiasis implies an infection with the nematode Dracunculus medinensis. It is not a filarial disease in the strict sense, as the worm is systematically only a distant relation of the filariae.

#### EPIDEMIOLOGY

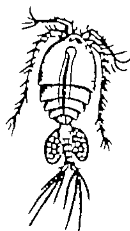
Dracontiasis is met with in Arabia, Iraq Persia, India, parts of tropical Africa, limited areas of America, in the West Indies and Brazil.

#### PATHOGENESIS

The life cycle of the Guinea worm again presents a remarkably specialized instance of parasitism the worm requires a crustacea and man as hosts for its propagation. Man acquires the infection by drinking water contaminated with the intermediate hosts—certain species of the water flea *Cyclops* The larvae of dracunculus require 7 to 10 days for developing in the coelom of cyclops, after which they become infective.

When ingested by man the cyclops is destroyed by the acid of the stomach juice but *the larvae of dracunculus are able to survive*, penetrate the stomach wall and enter the connective tissue spaces at the back of the peritoneal cavity Here they remain stationary without causing symptoms, until they have reached maturity Copulation takes place then, after which the male worm dies and is absorbed. The female

works its way into the corium of the skin of a part of the body which is likely to get into contact with the water usually the leg or foot. This migration takes place a long time after infection occurred generally not less than one year At the point where the pregnant female worm resides a blister forms at the ground of which the uterus of the worm protrudes When the limb is immersed in water the worm discharges live larvae which are swallowed by cyclops and a new life cycle has started The female worm dies after having discharged all larvae Measurements of the adult female 80–120 cm length, 1 6 to 2.2 mm diameter The male has never been found in man, but from experimental evidence seems to be much smaller The larvae are sheathless have a striated cuticle and measure 600 by 20 microns



653 Cyclops coronatus

## SYMPTOMATOLOGY

The subcutaneous appearance of the adult female worm is sometimes preceded by nausea, fever urticaria and other anaphylactoid symptoms —but the first sign of infection is in the majority of cases, the formation of a pemphigoid blister of 2–5 cm diameter This is typically situated over the malleolus of a foot, but in some cases it may appear

on the arm, scrotum, buttocks, the back (Indian water carriers) etc The blister soon ruptures, and a shallow ulcer is formed. The centre of this is seen—at close inspection—to be occupied by the tip of the worm from which a fine pellucid tube—the uterus—protrudes. When the limb is immersed in water or if water is applied by douching the uterus is seen to eject a milky fluid. Microscopic examination shows



654 Medina worm, the fiery snake that plagued the Jews on the Red Sea, the origin of Moses staff and Aesculapius attribute.
*(Beltran-Roussel Katzenellenbogen Simons)*

that this is swarming with actively moving larvae. The emission of larvae is repeated at intervals the worm produces an enormous quantity of them, and it takes several weeks before the uterus is completely emptied. During this time the worm becomes palpable and—in oblique illumination—visible, as a hard tortuous structure (like a cello string) in the cutis. After parturition is completed, the worm dies. It may become absorbed or calcified, if the infection is allowed to run its

natural course some aseptic inflammation usually accompanies this process

In most cases an attempt will be made to remove the worm. If this is done without sufficient care the parasite may be torn, or being elastic slip back under the skin carrying with it pyogenic bacteria which are invariably present in the ulcer from which it protrudes. The consequences may be sterile abscesses if the worm is ruptured subcutaneously or else a severe phlegmonous cellulitis Both are serious



655 D contusus adult female emerg g from third toe

complications In addition, the protein of the worm is highly toxic, and may produce fulminant anaphylactiod reactions Pyogenic infection tends to spread along the tunnel in which the parasite rests and to involve the whole extremity with complications, such as lymphadenitis arthritis and general septicaemia. Owing to these complications a number of cases of dracontiasis have ended fatally Infection by more than one adult worm is not rare [1]

#### PATHOLOGY

Sections of the blister under which the worm resides show a covering of detached epidermis and a granulating connective tissue at the

[1] Dr Jou and CAM re have described peritoneal localisat on t dracontiasis with symptoms of gastric ulcer

ground. The contents of the blister are a gelatinous exudate with numerous larvae. The worm lies almost entirely in the corium only the head and the uterus which protrudes from an opening immediately underneath it are free. The worm is usually surrounded by a fibrous sheath. After the death of the worm a moderately severe foreign body reaction occurs during absorption.

### THERAPY

The traditional method of removal practised in the East is to cause the worm to protrude as far as possible by repeated douching with cold water. With some skill it is then possible to wind the end of the worm around a stick, and by continued douching gentle traction and light



656. Medina worm protruding from the skin.
*(Katzenellenbogen-Jerusalem)*

massage from above downwards the worm is rolled up around the stick and extracted. This method requires skill and oriental patience and not so very rarely it fails. The worm is ruptured and the disastrous consequences described above may take place.

*Surgical dissection* of the worm, recommended by HAMILTON FAIRLEY, is a safe but cumbersome method. It incapacitates the patient for some time and produces extensive scars.

Injection of a 1 : 1 000 solution of *sublimate* (bichloride of mercury) into the subcutaneous portion of the parasite kills it and facilitates extraction, but it is not without objection as the solution used is

poisonous and highly irritating when injected subcutaneously and the danger of rupture of the worm remains. It should be mentioned that allergic reactions frequently occur after the death of the parasite (ephedrine, adrenaline, benadryl etc.).

*Phenothiazin*, a dye originally designed as a urinary antiseptic, is recommended by MASSON BAHR as a specific for D. medinensis infection. The substance is worked into a 10 emulsion with olive oil and wool fat, and four injections each of 10 ml. of the emulsion are given. The sites elected for treatment – two on the extensor and two on the flexor aspect of the leg—are anaesthetized with novocain, and the injections are applied subcutaneously at some distance away from



657 This case must be known for a medina worm emerging from the abdomen proved to be a suture which emerged spontaneously 6 months after an appendectomy

the worm. The sites are massaged after injection. Two courses are sufficient. The worm dies after 5–7 days; it can, under aseptic precautions, be extracted by the stick method.

### DIAGNOSIS

This should present no difficulty in the presence of a palpable and visible worm of considerable length under the skin. Inspection of the ulcer shows the end of the worm protruding, and douching produces the appearance of the uterine tube which voids a milky fluid swarming with larvae.

### PROGNOSIS

Favourable if complications are avoided.

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sac or sheath in which it can move backwards and forwards It con tains numerous nuclei and in the middle third some granular material or primitive gut There is a break in the cells anteriorly which repre sents the excretory pore and at the posterior end a similar gap denoting the cloaca *Microfilaria bancrofti* and *Microfilaria malayi* exhibit nocturnal periodicity migrating (apparently from the blood vessels of the lungs) to the peripheral blood in large numbers during the night being absent or present in small numbers only during the day time. In the Pacific there is a variety (known as *M bancrofti var pacifica*) the micro-



659 Microfilaria bancrofti

filariae of which are present in equal numbers both by day and by night.[1]

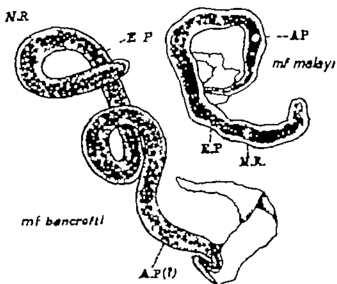
*Life-history* The embryos are taken up by various species of mos quito in the act of feeding The nocturnal form develops in various species of *Culex* and *Anopheles* The non periodic form in the Pacific is transmitted by *Aedes s scutellaris p seudoscutellaris*[2] The embryos in the stomach of the mosquito discard their sheaths and the sheathless larvae

[1] The probability is that this represents a distinct species—*W pacifica*—differing from the types by its minor morphological distinctions at the head and tail (of the female) (Manson Bahr)

[2] And *A. sc. polynesiensis*

pierce the stomach wall and come to lie between the muscles of the thorax. After undergoing two ecdyses they eventually grow into snake-like forms 1.5 mm in length and, travelling via the head of the insect, penetrate into the proboscis sheath whence they emerge onto the skin of man when the mosquito proceeds to feed The larval filaria then enters the lymphatic system and becomes mature very slowly in a period of three months or longer (WARTMAN)

*Wuchereria malayi* (BRUG 1927 RAO and MAPLESTONE 1940) is the




660 Microfilaria bancrofti and malayi (after Brug).
*(S ... Amsterdam)*

A.T — Anal pore
E.P — Excretory pore
N.R — Nerve ring

common form of filariasis in Malaya, Indonesia, Central India, Ceylon, S China and Indo China. The adult worms have seldom been found, but resemble those of *W bancrofti* in nearly every particular. The microfilaria has a nocturnal periodicity similar to those of *W bancrofti* The embryos have distinct characters being often found (in microscopical preparations) with head close to the tail and irregularly

disposed The tail tapers to a fine point and is continued as a fine thread There is one nucleus at the extremity Development in the mosquito takes place in the genus *Mansonoides* which are nocturnal feeders The larvae of these insects are adapted to live on certain water plants This parasite *(W. malayi)* has a rural distribution in Malaya.



661 Elephantiasis arabum. Note deep folds, a source of mycotic and pyogenic infections

*(Wolff Paramaribo)*

As far as is known the pathological effects produced by *W. malayi* are similar to those of *W. bancrofti*

The life-spans of the microfilariae and adult filariae are not accurately known. It is probable that the microfilariae can live in the blood stream unchanged for six weeks or longer and that the adults can

persist in the human body for about twelve years The number of embryos in the blood-stream is subjected to fluctuations from time to time, especially during some undercurrent illness such as typhoid or malaria, and they disappear entirely after an attack of lymphangitis and after presumably the death of the parent worms. The parent adult filariae frequently die in the lymphatic vessels and glands and there become cretified and they are found sometimes in large numbers These calcified objects become the centre of irritation and are invaded by giant cells and fibroblasts and eventually they become absorbed and microfilariae, then defunct, are destroyed in the substance of lymphatic glands and may be responsible for some pathological changes. They are broken up in the lymph node sinuses Microfilariae may also become imprisoned by proliferation of the endothelial cells of the lymphatic vessels which eventually leads to lymphatic blockage—a pathological fact of significance which indicates that the true basis lies in the destruction and blockage of the lymphatic filters of the lymphatic glands It has been conclusively shown by HAWKING and THURSTON that the microfilariae congregate in the smaller blood vessels of the lungs especially is this the case as MANSON suggested with the nocturnal microfilariae during the day time. Their accumulation in the lungs forms a reservoir from which they are emitted from time to time but what may be the agency which controls this timetable is by no means clear

PATHOLOGY

A factor which has to be taken into consideration is the appreciation that in most cases *W bancrofti* and *W malayi* are not pathogenic and that the microfilariae may be found, often in large numbers in the blood stream in association with good health. It may be asserted that the more numerous the microfilariae the less likelihood there is of any systemic disturbances

Generally speaking the filaria causes two types of disease—one caused by the varicosity of the lymphatics and the other by more or less solid oedema. Apparently in some instances the parent worm, or worms, sometimes coiled together in a bunch, may plug the thoracic duct and act as an embolus, or may give rise to inflammatory changes in the walls of the vessel leading to stenosis The afferent lymphatic

glands at some considerable distance from the actual seat of the parent filariae undergo considerable pathological changes such as fibrosis focal necrosis giant cell formation macrophage and histiocyte proliferation and aggregation of small epitheloid foci which are in the lymphatic glands and periglandular connective tissue The resemblance to tuberculoid focal granulomata may be very close indeed. Some microfilariae in the glands undergo calcification and thereby produce endothelial proliferative outgrowths into the lymphatic channels



662 Three year old elephantiasis in a woman girth 96 cm
*(Simons Amsterdam)*



663 Elephantiasis due to filaria bancrofti
*(Mellanby–Thadani)*

HARTZ (1944), who has given one of the best descriptions, sums up the picture as epitheloid-cell granulomatous lymphangitis. Different aspects of this essential lesion are found according to its age The epithelium of the vessel remains intact till the lumen becomes occluded. Small pseudo-tubercles may be found in the connective tissue.

## SYMPTOMATOLOGY

*Clinical manifestations* may be divided into three stages based upon the

pathological changes induced by the presence of the parent worms and the circulation of their toxins. These are (1) allergic manifestations during the stage of invasion, (2) the stage of deposition the lodgement of the parent filariae in the body and the liberation of micro-



664 Elephantiasis arabum so-called "pantalon de Zouave" or "plus fours leg" (*Aart–Caropen*)

filariae, and (3) the stage of fibrosis and the appearance of obstructive phenomena terminating in elephantiasis

1 The *allergic manifestations* have been well described by American observers in the Pacific area in soldiers and marines in the Second World War The onset is usually manifested by painful swellings of the scrotum, arms and legs, usually single or in combination. At times

*urticarial wheals* are noted Fever chills and malaise sometimes occur Fugitive tender painful swellings like *erythema nodosum* come and go Lymphadenitis of the cervical axillary and inguinal glands ensue. Common lesions also are funiculitis, epididymitis orchitis scrotal oedema and inflammation Hydrocele and varicocele are relatively common. Retrograde lymphangitis is common in the early stages and in association with obstructive phenomena such as lymph scrotum and elephantiasis It is often accompanied by an erysipelatoid spread and is



665 Elephantiasis of the arms and legs
(*Lichtbeel Reeders*)

colloquially known in British Guiana and the West Indies as the rose" Lymphangitis commonly affects the legs There is a characteristic painful cordlike swelling of the lymphatic trunks and associated lymph glands with red, congested, very painful streaks in the superadjacent skin and a high blood eosinophilia, suggestive of hyper sensitivity This attack may continue for several days and be accompanied by toxic symptoms, such as rigor severe headache and sometimes vomiting and delirium. After a time the tension of the in-

flamed lymphatics may be relieved by lymphous drainage from the surface. Usually the attack ends in general diaphoresis When the process affects an extensive abdominal varix it may produce symptoms of peritonitis and prove fatal—the so-called "filarial abdomen" "*Filarial Fever*" is another early manifestation, known in Samoa as "mumu" and in Fiji as "wanganga"[1] This fever sometimes also known as "elephantoid fever" occurs irregularly at intervals of months or years in nearly all forms of filarial disease. In its tendency to recur and its association with rigors and sweating it is apt to be



666. Varicose groin glands in filariasis bancrofti. Elephantiasis of the left lower leg also present

*(Simons–Amsterdam)*

confused with, or mistaken for malaria. It is after this form of "fever" that microfilariae commonly disappear from the blood.

2. *Second stage phenomena* are varied and consist of filarial abscess arthritis, synovitis, abscess of hip or knee joints, varicose groin glands, lymph scrotum, chyluria, hydrocele, chylous diarrhoea, chylous ascites.

*Filarial abscess* When the filaria dies it acts as an irritant and gives rise to a fixation abscess which becomes secondarily infected with streptococci or staphylococci. Such abscesses frequently occur in the

[1] In Surinam it is called "boubou" which means "swollen" as well as bogey man. Both homonyms are applicable since the filarial fever may very suddenly surprise the patient.

limbs or scrotum and will discharge in due course and sometimes may reach such large proportions that they have to be opened surgically It is possible that the starting point of the abscess is a haemorrhage occasioned by the adult filariae in the deeper tissues When suppu



667 Lymph scrotum in filariasis bancrofti

ration takes place in a joint cavity such as the knee or hip, it is a much more serious affair and in the chronic stage these distressing cases are apt to be mistaken for joint tuberculosis

*Varicose groin-glands* are frequently associated with lymph scrotum, with chyluria and chylous hydrocele These swellings may be of small

size, about that of a hazel nut, or may attain that of a clenched fist. Usually the inguinal and femoral glands are affected. The glands themselves are hard and fibrous and are surrounded by a layer of elastic lymphatic tissue. It is important that they should be distinguished from femoral or inguinal herniae for sometimes the two conditions may coexist. These swellings slowly subside in the prone position. When punctured with a syringe the lymph may reveal microfilariae or filarial ova. Unless they give rise to an incapacitating amount of discomfort they are best left alone, for excision is not satisfactory. Vari



668. Elephantiasis scroti in 9 year old Hindustani boy
*(Lampe–Paramaribo)*

cose axillary glands have been reported. Occasionally lymphatic varices are found on the surface of the abdomen, arms and legs. Lymphangiectasis of the spermatic cord is not uncommon.

After an attack of lymphangitis a line of induration remains and, on excision, cyst like dilatations of the lymphatics have been demonstrated. Enlargement of the lymphatic glands are the commonest manifestations of filarial disease in the Pacific. The epitrochlear glands at the elbow are almost invariably affected and may sometimes attain large dimensions. This may be taken as a diagnostic sign of filarial

disease. On dissection live filarial worms or their calcified remains may be demonstrated.

*Lymph scrotum.* The scrotum is usually enlarged and silky to the touch. A large number of smaller and larger lymphatic varices which have ruptured, discharge quantities of straw-coloured or blood-stained lymph. These "leaks" may continue for several hours staining the clothing. It is sometimes necessary to remove the scrotum, though usually palliative treatment with suspensory bandaging and frequent dustings with boracic powder are effective.





669–670. Elephantiasis of the penile skin and scrotum.
*(Wolff, Paramaribo* and *Sagher–Jerusalem)*

*Chyluria.* Is caused by a lymphatic varix (due to obstruction of the prevertebral lymphatics) rupturing the wall of the bladder or elsewhere in the urinary tract. The contents of the lymphatics escape into the urine and chyluria results. Often there is an admixture of blood and the condition is known as haematochyluria. The microfilariae may therefore be found in the urine where they were described by WUCHERER in 1866. Chyluria may appear without warning, though it is usually preceded by backache and pelvic pains. Retention of urine from the presence of lymphous clots may occur. Chylous urine re-

sembles milk, but it may sometimes be pink through admixture of blood. Chylous urine on standing separates into three layers.

An allied condition "lymphuria" is due to the discharge of lymph into the urinary bladder. The chief cellular constituent is the lymphocyte. *Chylous hydrocele is not unusual and may be associated with the* common filarial hydrocele. Chylous ascites of the peritoneum and chylous diarrhoea of filarial origin are very rare. Filarial orchitis funiculitis and hydrocele are frequently found in association. Attacks of filarial orchitis are acute and associated with fever and are usually accompanied by an effusion into the tunica vaginalis. The aspirated fluid is at first cloudy and contains large numbers of microfilariae. The



671 Elephantiasis vulvae et clitoris.

*(Swaen–Amsterdam)*

epididymis is enlarged and nodular. Calcified plaques and calcified filariae can frequently be demonstrated in the hydrocele sac. Filarial hydroceles may attain a large size and when of long standing they contain clear straw-coloured hydrocele fluid and microfilariae are not found. Under these conditions they are best treated by operation and stripping of the hydrocele sac.

*Filaria septicaemia.* A serious aspect of filarial infection is the susceptibility which it *evokes to secondary infections with pyogenic* organisms. The damaged lymphatic vessels become infected with *Streptococcus haemolyticus* which spreads to the blood vessels and septicaemia results.

3 *Elephantiasis* is the final expression of the third or obstructive stage of filariasis. It therefore can be considered as the outcome of hyperfilariation. In Cochin China about 5 per cent of the population is affected with elephantiasis, but it is even more frequent in the Pacific Islands, Samoa, the Ellice Islands and Tahiti for instance. In 95 per cent of cases the lower extremities are affected either alone or associated with a similar condition of the scrotum and arms. In the Pacific Islands the arms are commonly attacked although in other filarial regions this is very rare. Still more rarely the mammae, vulva and circumscribed portions of the trunk of limbs may be the seat of



6 2. Elephantiasis (Pantalon de zouave or plus fours leg) due to neurofibromatosis.

*(Prins—Jogjakarta)*

elephantiasis. In any of these situations elephantiasis commences with repeated attacks of lymphangitis, sometimes even with dermatitis and cellulitis accompanied by attacks of elephantoid fever. O'CONNOR made the interesting observation that the starting point of these reactions lies in focal spots which mark the site of dead or dying adult filariae.

On sectioning elephantoid tissue the dermis is found to be dense fibrous and hypertrophied. The subjacent connective tissues are blubbery and of a yellowish colour from lymph infiltration, so that on pressure a quantity of lymphous fluid escapes.

*Elephantiasis of the legs*[1] is usually confined to below the knee and is generally furrowed and redundant. The swellings may attain enormous dimensions so that the patient becomes anchored and immobilized. The filarial elephantiasis may thus be partially pyogenic. Treatment



673 Elephantiasis nostras due to recurrent erysipelas in clinical appearance resembling that produced by *B. bancrofti*

*(Orig. G. Coste-Bele Harlequin)*

of this condition is manifestly unsatisfactory. In the early stages where the oedema is soft and pliable a good deal may be done by crepe bandaging with porous rubber slips according to KNOTT's

[1] Elephantiasis arabum, Barbados leg, kakki gadja (Indonesia), *mal de Cayenne*, begi footoo (Surinam)

technique but this at best only affords temporary relief Various operative measures, such as Kondoleon's, Lanz's and Kondoleon's, which aim at restoring the lymphatic flow are impracticable under tropical conditions

*Elephantiasis of the scrotum* is the most distressing and remarkable of filarial manifestations. These scrotal tumours may attain enormous dimensions The largest recorded weighed 224 lbs The patient becomes completely anchored by the weight of the mass which may exceed that of the remainder of the total body weight The lymphatic groin glands are usually much enlarged and fibrosed and may also be varicose The tumour consists of two portions—a dense rind of hypertrophied skin and a mass of blubbery tissue in which testis cords and penis are embedded The blood vessels which supply the enormous growth are much hypertrophied and are apt to bleed freely This form of elephantiasis can be satisfactorily treated by operation. The details of the operative technique are too complicated to be gone into in this account

*Elephantiasis of the arms* is comparatively rare in most countries but is common in the Pacific where non-periodic filariasis is prevalent. Essentially it differs little from a similar condition of the legs. Little can be done in the way of treatment except by massage and bandaging

*Elephantiasis of the vulva and mammae* is also rare Tumours of both are best treated by operation The mammae especially in Samoans may attain enormous proportions and the organ may descend below the pubes to the knees

Elephantiasis of limited areas of skin, especially that arising from the anterior surface of the thigh, have been described from Fiji and British Guiana.

There is no evidence at present available that filariasis due to *W malayi* differs materially from that described for *W bancrofti* except for predilection for the legs

## THERAPY

In Hetrazan (or banocide, (I-diethyl-carbamyl-4-methyl piperazine hydrochloride)—we possess a drug that is specific for microfilaria of *W bancrofti* Evidence is still lacking that it is capable of injuring or destroying the adult worm in tissues Its action on the microfilaria is

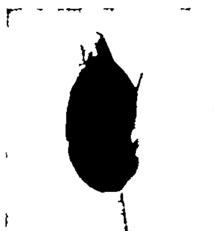
not direct, but as HAWKING and colleagues have demonstrated, it appears to modify the organisms in some way so that they are devoured by the phagocytes of the endothelial system and thereby removed from the circulation. The actual optimum dosage has not been finally settled and various workers have given it in a considerable range the principle being that small doses appear to be equally as effective as larger ones The range is from 0.2 to 7 mg per kg body weight. The usual dose is 150 mg daily to an adult man. The action is



674 Elephantiasis caused by *W. malayi* After operation
*(Fatel-San Francisco)*

almost immediate and the microfilariae begin to disappear from the circulation within a few hours. It has been established that patients with a great number of microfilariae are more difficult to sterilize than those with smaller numbers The present most generally accepted method aims at keeping up the treatment for three weeks to a month, after which the microfilariae disappear from the capillary blood for six months or longer though it is possible to demonstrate them in small numbers usually in the venous blood taken from the median

basilic vein In closed cavities such as hydroceles the microfilariae are unaffected by hetrazan treatment Apart from allergic reactions there appear to be few side effects from hetrazan treatment in bancroftian filariasis. Hetrazan treatment appears to have little effect upon the grosser manifestations of filarial disease



675 Pseudo-elephantiasis, actually Quincke's oedema of the penis following hetrazan therapy of filariasis bancrofti.

(5 mins 1 natural size)

**PROPHYLAXIS**

Prophylaxis resolves itself into mass treatment with hetrazan of all infected individuals wherever this can be satisfactorily accomplished Anti mosquito measures such as the destruction of breeding places of the mosquito vectors concerned, include the burning of coconut shells and husks in the Pacific Islands In Tahiti the West Indies and British Guiana residual spraying with DDT has been followed by excellent results

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CHAPTER 48

# CREEPING DISEASE, ERRATIC ERUPTIONS AND CONSTANT HELMINTHIASIS AND MYIASIS

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## INTRODUCTION

Although literature contains various attempts to classify cutaneous and subcutaneous myiasis and helminthiasis no uniformity has so far been attained in this respect

This is due to the fact that this classification has often been made on aetiological grounds whereas—and this applies quite definitely to dermatology—a subdivision based on clinical data would probably have led to more definite results Thus one often sees creeping disease being confused with the more general concept of cutaneous myiasis and even *linear dermatoses being called "creeping eruptions" on account* of their being caused by a creeping insect whereas the eruption as such no longer changes and should not, therefore, be called "creeping"

Myiasis might also be subdivided histologically into epidermocutaneous and subcutaneous forms but this subdivision would give rise to undue overlapping and would therefore, be doomed to failure from the start. It is for these reasons that a clinical classification is to be preferred

## DEFINITIONS

But before proceeding to a discussion let us give a few *definitions*

I By *cutaneous* or *furunculoid myiasis* we understand that group of dermatoses which are caused by the presence of larvae of certain muscoid flies in the skin Among these flies are Musca domestica or common

housefly Sarcophaga or "flesh-fly" and the Oestridae ("bot" or "warble" flies) which lay hundreds of eggs in open wounds. On hatching out, the larvae feed on the rotting tissue, in some cases even involving the bone (especially Cochliomyia hominovorax) Possible allergic reactions such as urticaria, which may happen to arise in consequence, are not, of course, classed as myiasis although they are closely associated with it.

II By *cutaneous helminthiasis* we understand that group of dermal phenomena which are caused by the larvae of certain nematodes or threadworms

In view of the fact that the clinical phenomena of myiasis and helminthiasis are usually called by the same names, while it would be a Sisyphean task to fight against this now current nomenclature it will be more efficient to bring this customary classification under the dual heading *cutaneous helmintho-myiasis* [1]

III By *creeping disease* we understand that form of either cutaneous myiasis or helminthiasis which is caused either by larvae of insects, or by certain nematodes and in which the phenomena, actually "gain ground" completely satisfy the concept "creeping"

IV In contradistinction to this we understand by "*erratic eruption*" an affection which may appear here and there on the body according to whether the morbific parasite (be it not per continuitatem, as in the case of creeping disease) has moved to another area of the skin.

V By *constant cutaneous myiasis* or *helminthiasis* we understand that form which remains stationary

Now if we classify the various larvae and vermes under the headings "creeping" "erratic" or "constant" myiasis, or helminthiasis, we get the following scheme

[1] Schistosoma dermatitis does not belong to this group, since it is caused by trematodes and is not generally classed among the group of diseases which we are discussing here

| Creeping | Erratic | Constant incl. ophthalmo-myiasis |
|---|---|---|
| *Myiasis* | *Myiasis* | *Myiasis* |
| I. Oestridae<br>A. Hypoderma bovis et lineata<br>B. Gastrophilus haemorrhoidalis et ... terinus | None | I. Oestridae<br>A. Dermatobia cyaniventris (ver Macaque)<br>B. Rhinoestrus purpureus<br><br>II. Sarcophagidae<br>A. Cochliomyia hominivorax et americana<br>B. Chrysomia bezziana<br>C. Cordylobia anthropophaga<br>D. Wohlfahrtia magnifica<br>E. Lucilia caesar et sericata |
| *Helminthes* | *Helminthes* | *Helminthes* |
| Ancylostoma braziliense<br>Ancylostoma stenocephalum<br>Ancylostoma caninum | Loasis (calabar swellings)<br>Gnathostomosis spinigerum | Onchocerciasis (ol. volvulus)<br>Dracontiasis |
| | | *Acarinae* |
| | | Scabies — Rhizoglyphus — tetranychus |

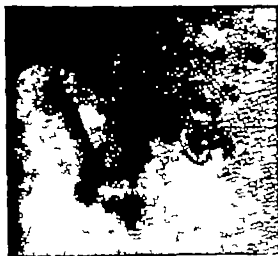
## SYMPTOMATOLOGY

### CREEPING DISEASE

Creeping disease also called *myiasis linearis* or *larva migrans* (LEE) is marked by the presence of an itching, stripe formed bullous lesion extending day by day by as much as 1–3 cm the blister fades away at the initial extremity leaving a trace of erythema. As a rule there are no scars. The bullous line, which may show various capricious twists, may be interrupted here and there, which gives it the appearance of an irregular necklace. The larva precedes the visible phenomenon, *i.e.* the bulla comes up where the larva has been just before. In most cases therefore the larva is not found in the visible burrow but one or two centimetres further on. Since one can only guess at the direction of the

burrow it is not easy to find the larva but it can be done in some cases by softening the skin with oil immediately around the newest extremity of the stripe, which renders the thereby macerated horny layer slightly transparent, when the larva may be observed with the aid of a strong eyepiece. The stripe lengthens at a pretty fast rate, but shows no ramifications unless there are several larvae at work, when the skin of the affected part becomes traversed by a large number of zig zag lines

Sites of predilection are the legs and the buttocks, but the arms may



676. Creeping disease of the thigh.

also be affected. One of us (S) once saw two soldiers wearing shorts who had been hiding under an army truck for twenty-four hours during this time the extensor sides of both their upper legs had been involved by creeping disease to such an extent that they looked like maps covered with roads and railways.

The *incubation period* is about a month. MANSON BAHR has described a case with an incubation period of three months

**AETIOLOGY**

The following organisms are to be held responsible for creeping disease

I *The Oestridae or bot flies* they are large flies resembling bees and exist particularly in the tropics They include Hypoderma bovis and Hypoderma lineatum—which may also be found in the eyes (see ophthalmomyiasis) and Gastrophilus haemorrhoidalis and Gastrophilus veterinus Hypoderma chiefly attacks cattle only rarely man. Since the



677 Creeping disease of the hand

*([illegible])*

larvae hatch out on the healthy skin they may burrow into the buttocks or thighs of a rider instead of into the host.

Gastrophilus occurs more frequently in horses (also in horses intestines) Both riders and grooms—if not already attacked by the fly itself—may be infected.

II The *Ancylostomata* occur not only in the tropics, but also in Florida and sub-tropical Russia They include Ancylostoma brasiliense, A. ceylonicum, Agamonematodum migrans (with dogs and cats as hosts) Ancylostoma stenocephala, and Ancylostoma caninum. The

Ancylostomata make shorter but often more numerous, burrows than the Oestridae.

"*South African creeping disease*" or *sandworm disease* is probably due to an acarus Tetranychus molestissimus it is not however a true "creeping disease"

## ERRATIC ERUPTION

In contradistinction to creeping eruption, in which one can follow the course of the burrow through the skin, the provoking agent of erratic eruption will disappear from the lesion, to turn up again a day or so or even much later in an altogether different part of the skin Erratic eruption is never caused by any form of myiasis, only by Filaria loa and Gnathostomosis spinigerum (South-East Asia) In the former



678 Creeping disease of the finger
*(V. an der Zyl-The Hague)*

case the swellings may be only an urticarial reaction due to the loa infection.

*Gnathostomasis spinigerum* is a nematode worm about 1–5 cm long which may infest the coat of certain animals stomachs (cats snakes etc.) setting up cysts. It is rarely found in man, when it causes a furunculoid process which becomes necrotic in the centre. A creeping or an erratic, eruption may then occur in the skin (in some cases in the pharynx) The intermediate host between man and animal is probably a cyclops or freshwater fish, Clarias batrachus.

## CONSTANT HELMINTHIASIS OR MYIASIS

Finally there are certain forms of myiasis or helminthiasis which are often called creeping" but which are neither creeping nor erratic, but

remain constant, *i.e.* they do not change their place apart from the possible extension of their area. The following belong to this class:

A. *Oestridae* or *"bot flies"* including:

Dermatobia cyaniventris found in South America. The female deposits her eggs on wet plants. The eggs stick to flies and mosquitoes that come to the pools to feed; the insects transmit them to man and beast where they hatch out, after which the club-shaped larva called *"ver macaque"* or *ver moyocuil* (Mexico) (also called *Berne, Torsel* and *Gusano*) bores into the skin settling up painful nodules or furunculoid boils from which on pressure oozes a sero-purulent, sometimes black, fluid. This *"mosquito worm"*—as it is called in Surinam—may be found in dogs, cats, and cattle.

Rhinoestrus purpureus is found chiefly in horses around the Mediterranean. It occasionally appears in the human eye when it hides under the conjunctiva.

B. *Sarcophagidae* or *"flesh flies"* and *Muscideae* or *house (field-) flies*

The most important of the Sarcophagideae is Wohlfahrtia or Sarcophaga magnifica, the flesh fly, which deposits its eggs in wounds and sores. It is found practically everywhere. Sarcophaga haemorrhoidalis provokes intestinal myiasis. Sarcophaga carnaria lays its eggs in the vagina. Other Sarcophagideae are S. lambens and S. prophila (Brazil), S. plinthopyga (Dominican Rep.), S. ruficornis (India), etc. Cochliomyia hominovorax or americana, or macellaria, which, in fact, is one of the muscideae, occurs in N. America and Argentina, but only during the hot season. There is also a genus described by DEPIED and BAURAT in Indo-China, *i.e.* Chrysomyia bezziana. FIELD and WISE described Compsomyia violacea from the Guianas. Cochliomyia hominovorax is marked with three stripes on its back; it has a range of action of between six and twelve miles; the female lays hundreds of eggs in open wounds, nose and ears of dying persons and animals. The larvae (called *"screw worms"*) eat their way into the tissues, not even sparing the bone; eventually arriving in the brain they may cause death. The blue-coloured Chrysomia bezzania with its green-coloured thorax, which occurs mainly in South-East Asia, prefers living tissue, *e.g.* the nose, for its breeding place. Cordylobia anthropophaga, called *"tumbu fly"* in Africa, is yellow with brown wings. Its behaviour resembles that of Dermatobia cyaniventris. The larva is named *"ver du cayor"*. It

does not reach the skin by insects as does the "*ver macaque*" but by dry sand via the subject's clothes

C. *Helminths*

As regards constant helminthiasis, we refer the reader to the chapters dealing with onchocerciasis and draconitiasis. It appears that cutaneous helminthiasis may also be caused by Cysticercus cellulosae, the vesicular form of Taenia solium. This affection, called *ladrerie*, is characterized by multiple painless nodules containing parts of the Taenia. Sparganosis—a very rare disease—is caused by Sparganum mansoni (or Bothriocephalus liguloides or B. mansoni), a worm which frequents the intestines of dogs and cats (Japan, the rest of East Asia, and many tropical regions). The larvae may occur in man in the peritoneal or pleural cavity, in the ureter and under the conjunctiva. In some cases the "tumours"—which, for that matter, are indolent—are more or less superficial; they are at any rate of short duration (*e.g.* two weeks). See also Chapters 41 and 45.

D. *Acari*

Although, as we mentioned above, skin affections caused by acari should not be classed among either myiasis, helminthiasis or creeping eruption, this is nevertheless often done. Tetranychus molestissimus, which is mostly found between the toes (South America and South Africa), slightly resembles tungiasis.

Rhizoglyphus parasiticus is responsible for a similar affection chiefly in coolies on tea estates.

## OPHTHALMO-, NASO- AND AUROMYIASIS

The organisms which select the conjunctiva as their predilection place are the Myodaria and the Oestridae: Hypoderma, Rhinoestrus, Oestrus ovis (in shepherds), and Gastrophilus equi. Especially Wohlfahrtia magnifica—one of the Sarcophagideae—may provoke a painful conjunctivitis. Cochliomyia, Chrysomyia, Calliphora and Anthomyia frequent the ears.[1]

[1] An "eye-fly" which is not one of the Muscoid and does not cause myiasis, is Hippelates pusio (one of the Oscinidae or Chloropidae). It is closely akin to Hippelates pallides which feeds on ulcers. When this happens in the case of yaws ulcers, spirochaetales may be found in the oesophagus.

remain constant *i.e.* they do not change their place apart from the possible extension of their area The following belong to this class

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Dermatobia cyaniventris found in South America The female deposits her eggs on wet plants. The eggs stick to flies and mosquitoes that come to the pools to feed the insects transmit them to man and beast, where they hatch out after which the club-shaped larva called "*ver macaque*" or *ver moyocuil* (Mexico) (also called *Berne Torsel* and *Gusano*) bores into the skin setting up painful nodules or furunculoid boils from which, on pressure oozes a sero-purulent, sometimes black, fluid This "*mosquito worm*"—as it is called in Surinam—may be found in dogs cats, and cattle

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Bedbugs, ticks, caterpillars, etc. may cause dermatitides but they cannot be classed among the affections discussed in this chapter.

## THERAPY

The treatment of creeping eruptions is, as a rule, fairly easy. The zone within which extension of the burrow may be expected is frozen with ethyl chloride; if necessary this is repeated a week later. In most cases the affection will then be cured. If this treatment proves unsuccessful after being repeated two or three times, then a small piece in front of the burrow must be cut out. Erratic helminthiasis should be surgically removed. Constant open myiasis is treated with disinfectants.

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# OXYURIASIS

## (Enterobiasis)

## (Pin–worm pruritus ani)

R. D. G. Ph. SIMONS
Amsterdam

### DEFINITION

The commonest and least dangerous, although most obstinate intestinal helminthiasis, which often results in a lifetime's periodically relapsing pruritus ani is oxyuriasis due to the thread- seat- or pin worm Enterobius or Oxyuris vermicularis (Linnaeus 1758).

By the time the patient consults the physician, on account of his or her sleepless nights and exasperation because of the itching, the pin-worm, as if "by intuition" disappears from the anal surface, which tempts the doctor to diagnose the condition as a symptom of prostate cancer, psychological conflicts from youth, etc.

The only cause dating from youth, in fact, is the pin-worm, which may infest 50 per cent or more of the children in some schools. By the time the patient goes off to sleep the pin-worm wakes up and causes a pruritus for which the patient unconsciously scratches himself. In doing so he infects his nails with the eggs, which in their turn are brought to the mouth and so into the intestines. Oxyuriasis is a familial disease, found more particularly among children – very probably because they are more readily examined than adults.

### EPIDEMIOLOGY

Although Enterobius vermicularis is found everywhere, it seems to be found less in the tropics. This is almost certainly due to the more regular bathing and/or to anus washing in those regions where this is customary.

**AETIOLOGY**

Enterobius vermicularis is a minute, white nematode, the male being half as long as the female. The male has a coiled posterior extremity It is less frequently found than the female, as it usually dies in the caecum. The female has a pointed extremity and is 0.5–1 cm. long The female migrates to the anus, but the worm may also be found in the anal groove and in the underwear The *eggs* in clusters, are 30–60 microns, and have a double wall. They can also be found in the anus and anal groove and when they have fallen off they may be found on the floor or the furniture, and particularly on doorknobs The embryo is usually visible through the transparent shell" of the eggs. Eggs are rarely found in the faeces.

Although multiplication of the parasite is most probably possible only in the intestines, the life-cycle includes the fact that the eggs are swallowed from infected fingers. The larvae hatch out in the duodenum, and pass through the intestines to the caecum, rectum and anus, where they develop into the adult form. The whole cycle takes about 2 months (NAPIER)

**SYMPTOMATOLOGY**

Oxyuriasis may be present without any outward sign but a number of conditions are regarded as possibly caused by the pin-worm Pruritus ani is the commonest feature but fluor albus in girls, or so-called pertes blanches" (white stains) in the panties are almost pathognomonical for enterobiasis. Pruritus vulvae (leading to masturbation) and salpingitis may be caused by pin-worms. Irritability is not the cause but the sequel, as is also sleeplessness. Pin-worms may be found in intertrigo near the genitals or in the anal groove. Scratching, and thereby inoculation of the crushed worms and eggs may set up local allergic reactions (CIESZYNSKI)

**DIAGNOSIS**

The most effective way to arrive at the diagnosis is regular, thorough examination over a period of a few months. Eggs will hardly ever be found in the stools. A popular method of investigation is the "swab" or the "tape method, by which a glass rod with a piece of cellophane is wiped around the anus. The cellophane will catch the eggs, which

are then applied to a slide by a few drops of water dropped on to the cellophane. Strips of cellophane tape applied to the anal surroundings may also catch eggs. We advise our patients to have their anus examined every night for the actual pin worms and to pay close attention to their toilet paper after use. It may then happen that pin-worms are reported after this having been done for weeks in vain.

A skin test with Enterobius antigen may be helpful in making the diagnosis.

#### THERAPY

The therapy of oxyuriasis requires considerable energy over a long period. Since the pin worm lives in the intestines, internal treatment is necessary. This can be done by oral treatment, giving the patient one gram tablets of gentian violet three times daily before the meals *for a two weeks period. Phenothiazine therapy (dangerous for children* under five years) three times daily 0.500 to 2 gram for 5 to 7 days. The papain-drug Velardon (ORGANON, Holland) has proved valuable.

If the patient is given fatty ointments for his complaints the condition will only get worse and eventually the patient, tormented by both pin worms and doctors, may be regarded a "psychological" or even become a psychiatric case.

During intervals between the relapsing condition, the latest drug may be considered to be the right one, but this may depend on the caprices of the pin worm, which at any time may shatter our illusions.

#### PROPHYLAXIS

Since oxyuriasis is a familial disease, and even a school disease, every member of the family affected and every pupil of the school concerned should be regularly examined. Personal cleanliness is imperative. Providing panties for the children, in order to avoid or mitigate scratches, is also necessary. (See also page 117 and the Addenda at the end of this book.)

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# DISEASES DUE TO FUNGI

CHAPTER 50

# MEDICAL MYCOLOGY

## (Introduction)

R. D. G. PH. SIMONS – Amsterdam

N. GOHAR – Wembley Park (England)

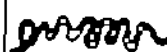
A multiplicity of names have been applied to mycotic diseases. This is due to the fact that one and the same infection can sometimes present different clinical appearances and that clinically similar mycotic affections may be caused by various fungi.

The term "*dermatomycosis*" intended to cover all superficial fungous affections of the skin, was originated by VIRCHOW (1865) while DARIER used this name exclusively for fungous infections which could also penetrate the skin. Present-day books consider dermatomycoses as skin diseases caused by a group of closely related fungi, namely the dermatophytes, collectively termed "*teignes*" by the French. These may affect the skin, hair and nails. SABOURAUD includes here (clinically) favus trichophytosis and microsporosis, which he regards as one single group of "*parasites mycéliens*"

Generally the dermatomycoses are classified according to the part of the body on which they occur Thus, one speaks of *onychomycosis* when the nails are affected, and of *trichomycosis* when the hair is affected.

There are also fungous affections which are limited exclusively to the hair, such as the trichomycosis in the narrower sense, (*e.g.*, lepothrix formerly called palmellina) and there are the epidermomycoses such as erythrasma and pityriasis versicolor which are confined to the skin.

The English term "*tinea*" (= worm-eaten) comprises all diseases





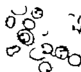














680 Cultural characteristics of the most important pathogenic fungi.

of the skin, hair and nails including the dermatomycoses and affections of the skin caused by fungi sometimes entirely different from dermatophytes

In this introduction to clinical mycology a new and practical classification is attempted

*Classification of the vegetable kingdom*

I *Spermatophytes*
II. *Pteridophytes*
III *Bryophytes*
IV *Thallophytes*

In the Thallophytes no blade, stem or root can be distinguished They are divided into I Algae, II Lichens, III *Mycetes or Fungaceae*

The mycetes contain no chlorophyll, and elaborate their nutriment as saprophytes from dead organic substances or as parasites on living organisms. They are subdivided into (a) *Eumycetes* or *Fungi* (b) *Myxomycetes* (c) *Schizomycetes* (bacteria including *Actinomycetes*)

Of all these only the pathogenic *Eumycetes* and *Schizomycetes* are of medical importance.

*Fungi or Eumycetes*

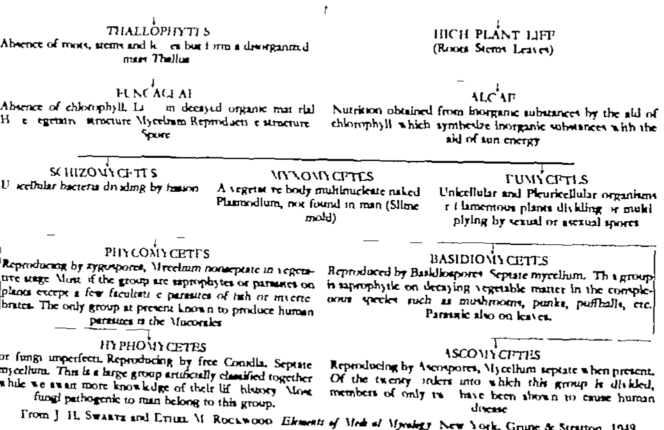
The body of the fungus consists of the *thallus* made up by a mat of *mycelia* and an *aerial part* comprising sterile and fertile mycelia, the latter called *sporophores*

The hyphae may be subdivided into cells by septa, and they may by various methods develop *spores* which are responsible for the propagation of the species. The shape and mode of origin of the spore and the sporophores are important characteristics in the classification of the fungi into the different groups

The fungi are divided into

1 *Phycomycetes* the hyphae have no septa they are of little medical importance.
2. *Ascomycetes* after fusion of nuclei during fertilization, asci are formed, in which ascospores develop by free cell-formation each ascus generally contains eight ascospores
3 *Basidiomycetes* the spores which develop after fertilization are formed exogenously on a special sporophore, the basidium there

The following chart by SWARTZ* is a diagrammatic sketch which serves to illustrate the origin of fungi.




From J. H. SWARTZ and EMILY M. ROCKWOOD: *Elements of Medical Mycology*. New York, Grune & Stratton 1949

are generally four spores on each basidium. Most of the mushrooms belong to this group

4 *Hyphomycetes or Fungi imperfecti* propagated solely by asexual spores This group comprises fungi of which the perfect or sexual form has not been discovered

Fungi are given a generic and a specific name followed by the name of the author who first described the fungus *e g Penicillium notatum* Westling Sometimes the name of the fungus is followed by the names of two authors *e g. Trichophyton rubrum* (Castellani) Sabouraud. This indicates that CASTELLANI first described this fungus (as *Epidermophyton rubrum*), while SABOURAUD transferred it later to the genus *Trichophyton*

*Phycomycetes*

This group is of little medical interest except for the genus *Coccidioides* which is difficult to classify systematically It was formerly included among the protozoa. BRUMPT's view is that *Coccidioides* is still most closely related to the Phycomycetes The species *Coccidioides immitis* Rixford and Gilchrist which causes coccidioidomycosis may belong here. The majority of fungi of medical importance belong to the *Ascomycetes* and to the fungi imperfecti

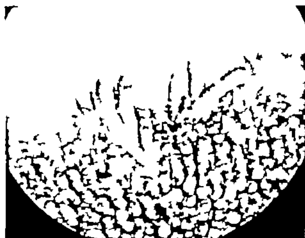
*Ascomycetes*

These fungi propagate not only by ascospores (sexual spores), but also by asexual spores which develop on spore-bearers. The genera *Penicillium* and *Aspergillus* are included among the *Ascomycetes* because the ascus form of a number of species exists. Fungi of this genus are generally found in nature on organic substances the spores are found in abundance in the air and can cause troublesome contaminations in the laboratory

The species *Aspergillus fumigatus* Fresenius which is found in the soil can be pathogenic in the lungs

Also of medical importance is the *Ascomycete Piedraia hortai* (Brumpt) Fonseca et Leao the cause of black piedra. The so-called white piedra is caused by one or more species of the genus *Trichosporon* It is probable that the various species described as causing this affection are all identical with *Trichosporon beigelii* (Rabenhorst) Vuillemin.

To the Ascomycetes belong also the Saccharomycetes or ascosporogenous yeasts ("levures ascosporées") These are unicellular organisms which multiply by budding. A number of yeasts, however, do not produce ascospores ("levures anascosporées") The latter are also called *blastomycetes*, although the prefix *blasto*, implying "budding" is actually applicable to both forms. The anascosporogenous yeasts are often classified in the following section of fungi imperfecti. Concerning the term *blastomycoses* most of these conditions are not caused by blastomycetes, but by dimorphic fungi ("*états* lévuriformes"), which only reveal a yeast like stage in the human host, and not in culture. See Chapter 71



681 Ascomycetes from the nodule of black piedra

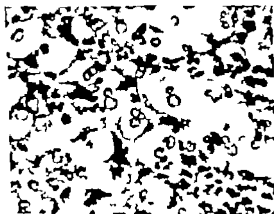
To the group of the best known blastomycetes, *e.g.* *Candida* (erroneously also termed *Oidium* or *Monilia*, since these are of an entirely different order) belong a number of pathogenic species: *C. albicans* on mucous membranes, *C. tropicalis* and *C. pseudotropicalis* in the lungs, *C. krusei* in the intestines, *C. guilliermondi* on hair and skin, and *C. parapsilosis* affecting skin and nails. These fungi are found principally on mucous membranes and skin, in interdigital spaces and may sometimes affect the internal organs.

Pathogenic yeasts of other groups to be mentioned are *Cryptococcus neoformans* (Santelice) Vuillemin (syn. *Torulopsis neoformans* (Sanfel

ice) Redaelli the cause of torulosis and *Blastomyces dermatitidis* Gilchrist and Stokes which causes the North American blastomycosis or Gilchrists disease, and is morphologically and antigenically related to *Histoplasma capsulatum* Darling

*Fungi Imperfecti*

Facultative parasitic moulds are met with in different groups of fungi imperfecti. A fungus can sometimes be isolated repeatedly from a skin affection, although the species may not be actually pathogenic, as in the case of species of the genus *Cephalosporium*



682. Round, ovoid and budding yeastlike organisms of Cryptococcus neoformans or Torula histolytica.

(*Fasel Sea F mulsion*)

A number of pathogenic species have been described as belonging to the genus *Geotrichum* causing affections of the respiratory and alimentary tracts It is possible that these species are identical. Much uncertainty however prevails here. Further examples of pathogenic fungi imperfecti are enumerated below

*Sporotrichum schenckii* Matruchot causes affections of the skin and subcutaneous tissues.

Chromomycosis is caused by various fungi including *Hormodendrum pedrosoi* Brumpt, *Hormodendrum compactum* Carrion, or *Phialophora verrucosa* Medlar

The name chromoblastomycosis should, according to LANGERON be excluded from the literature, as this affection is not due to yeasts.

Various species of the genera *Madurella* and *Indiella* have been isolated from cases of maduromycosis.

*Histoplasma capsulatum* Darling is the cause of histoplasmosis. The fungus appears as a yeast in the tissues of the patient. In cultures however this fungus can be distinguished from all other pathogenic organisms by its large round to oval chlamydospores, whose walls have numerous blunt protusions.

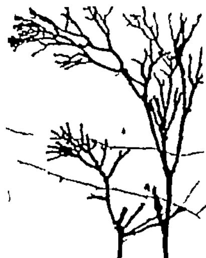
The lagest and morphologically most varied group of pathogenic fungi are the dermatophytes or *Trichophytoneae*. A perfect or sexual



683 Long branching hyphal strands segmenting into columns of arthrospores. (*Marshall Dowding*)

spore form is not known with any certainty to exist here. These fungi multiply solely by means of asexual spores, a large number of which have been described by SABOURAUD and assigned to various genera. EMMONS has reduced the number of these genera to three, and has also greatly reduced the number of types of spores. The dermatophytes propagate by means of two varieties of asexual spores: *microconidia* also called *aleurospores* and *macroconidia* or *fuseaux* by French authors. Chlamydospores may also be met with. The microconidia are unicellular round to oval or pear shaped bodies, which are borne laterally or terminally on the spore bearing hyphae. The base of the spore is broad, and under high magnification one can usally see the

collar" where the spore was attached to the hypha. The number of conidia may be so great that the culture has a sprinkled, powdery appearance, as in *Trichophyton mentagrophytes* The macroconidia are elongated and are divided by septa into a number of cells. Three types of macroconidia are found in the dermatophytes, and this is the basis of Emmons division of the group into the three genera *Trichophyton* *Epidermophyton* and *Microsporum* The macroconidia of *Trichophyton* are baton-shaped, the end is rounded and the walls are thin



684 Favic chandeliers in Tr schoenleini
*(Marshall-Dundee)*

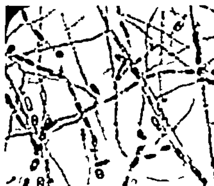
and smooth. The number of macroconidia varies with the strain and with the cultural conditions, and they may be entirely absent.

The genus *Epidermophyton* is represented only by the single species *E floccosum* It has only macroconidia which are oval in shape, blunt, bicellular or multicellular and possess a fairly thick wall. The macroconidia of *Microsporum* are fusiform and pointed, and may have up to fifteen septa. The external wall is thick and sometimes rough. Some dermatophytes form pigment in culture this is red with *T rubrum* and *T megnini* yellow to brown in strains of *T mentagrophytes* and

violet in *T. violaceum*. Pigment formation is variable and is largely dependent on the medium used.

*Pleomorphism*

Many dermatophytes lose their distinctive characteristics after some time in culture, spore formation becomes scanty or ceases, the aerial hyphae becomes predominant and they become pleomorphous. This process of pleomorphism is irreversible.



685. Septate hyphae and chlamydospores in cultures of C. immitis
(*Stewart. Berkeley-Calif.*)

*Dermatophytes*

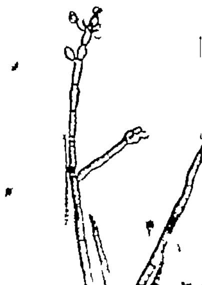
The following dermatophytes are frequently met with:

I. *Trichophyton* (affects hair, skin and nails).
*T. mentagrophytes* (Robin) Blanchard (syn. *T. interdigitale* Priestley, *T. gypseum* Bodin, *T. granulosum* Sabouraud, *T. felineum* Blanchard, *T. equinum* Gedoelst, the Kaufmann Wolf fungus).
*T. rubrum* (Castellani) Sabouraud (syn. *Epidermophyton rubrum* Castellani, *T. purpureum* Bang, *T. marginatum* Nuys). This species is spreading from the East progressively over Europe.
*T. tonsurans* Malmsten (syn. *T. crateriforme* Sabouraud, *T. umbilicatum* Sabouraud).
*T. epilans* Boucher and Megnin (syn. *T. flavum* Bodin, *T. cerebriforme* Sabouraud).

*T Sabouraudi* Blanchard (syn. *T acuminatum* Bodin, *T pilosum* Sabouraud)

*T sulfureum* Sabouraud

*T schoenleini* (Lebert) Langeron *and* Milochevitch. (syn. *Achorion schoenleini* Remak, *T album* Sabouraud, *T discoides* Sabouraud) causes favus and gives a plicated waxy culture



686. Hormodendron pedrosoi: microconidia of hormodendron type.
(*Gonzalez Ochoa Mexico*)

*T concentricum* Blanchard (syn. *Endodermophyton concentricum* or *tropicale* Castellani)

*T ferrugineum* (Ota) Langeron and Melochevitsch (syn. *Microsporum orientale* Carol)

*T violaceum* Sabouraud (syn. *T glabrum* Sabouraud, *Achorion violaceum* Bloch)

*T megnini* Blanchard (syn. *T roseum* Bodie, *T rosaceum* Sabouraud)

II *Epidermophyton* (affects skin and nails)

*E. floccosum* (Harz) Langeron and Melochevitsch (syn. *E. inguinale* Sabouraud and *E. cruris* Castellani and Chalmers)

III *Microsporum* (affects skin and nails)

*M. audouini* Gruby (syn. *T. decalvans* Malmsten, *M. velveticum* Sabouraud) is one of the causes of tinea capitis in children.

*M. gypseum* (Bodin) Guiart and Grigorakis (syn. *Achorion gypseum* Bodin, *M. fulvum*)



687 Endospore-filled ascus of coccidioides immitis in tissue. *(Fatal San Francisco)*

*M. canis* Bodin (syn. *M. felineum* Fox and Blaxall, *M. equinum* Guégeun, *M. lanosum* Sabouraud)

*Actinomycetaceae or Microsiphoneae*

Actinomycetaceae should be regarded as forming a transitional group of organisms between the Schizomycetes and the Eumycetes. They bear a great resemblance to bacteria and are therefore classed by most workers among the Schizomycetes. LANGERON states that if

they are fungi then the Mycobacterium of tuberculosis and that of leprosy are also fungi, and that if tuberculosis and leprosy are bacillary diseases, then actinomycosis is also a bacillary disease. A preparation of a culture of Actinomyces viewed under high magnification shows thin branched, sometimes spirally wound hyphae which separate into small spores. The aerobic producing actinomycetes are termed *Nocardiae*



688. Septat mycelia and microconidia in microculture of Sporotrichum schenckii.
*(Weichardt–Tübingen)*

The pathogenic species *Actinomyces bovis* Harz (syn. *A israeli* Dodge) is anaerobic, Gram-positive and non-acid fast. Some of the aerobic actinomycetes too are of medical importance. They belong to the genus Nocardia. *N asteroides* (Eppinger) Blanchard is acid-fast and has been isolated from lung affections. *N maduraе* (Vincent) Blanchard which is one of the many causal agents

of Madura foot. *A. somaliensis* affects the bone, whereas *A. madurae* does not. *Nocardia minutissima* Burchardt, the cause of erythrasma has not as yet proved capable of being grown artificially.

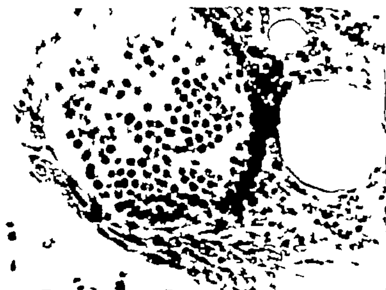
For the sake of conciseness each species of the dermatophytes will mostly be given only one synonym here. CONANT's book entitled "*Manual of Clinical Mycology*" actually gives eighteen synonyms for *Trichophyton mentagrophytes*. There is no unanimity of opinion yet as to whether all these eighteen species are in fact absolutely identical or that some of them are completely different varieties of the same



689. Nocardiosis: ray fungus of Nocardia mexicana in tissue.
*(González Ochoa—Mexico)*

species. There are many problems still unsolved in the literature on medical mycology. It frequently happens that a single pathogenic organism is indicated by a large number of different names. The description of pathogenic organisms is frequently so incomplete that it is extremely difficult to determine where to place a given organism in the classification of fungi, and whether it has not already been described under another name. This applies just as much to the dermatophytes as to the yeasts and also to the pathogenic organisms of various other groups of fungi.

Determining the correct name of a fungus or Actinomycete requires a wide knowledge of forms and a fundamental acquaintance with the rules of botanical nomenclature. Frequently the mycologist is not familiar with the morbid manifestations which the fungus causes while to the practising physician the domain of fungi is generally still a dim labyrinth[1] Hence the great confusion that still prevails in many territories of medical mycology



690 Spore-filled sporangium of rhinosporidiosis in tissue.

*(González Ochoa—Mexico)*

## MYCOLOGICAL TERMINOLOGY

*Aerial* – living above the surface.

*Aleurospore* – a simple lateral conidium.

Cf. "La chronique scandaleuse scientifique (mycologique)" in De Bary, A., *Morphologie comparée et la biologie des champignons, mycétozoaires et bactéries* (1884).

The definitions have been taken from Jacob H. Swartz, *Elements of medical mycology* publ. by Grune and Stratton, New York 1949

*Arthrospore* – structure formed by segmentation of a hypha into a chain of cells at first cuboidal and later rounded

*Ascomycete* – fungus in which the spores are borne in saclike cells called asci

*Ascospore* – spore borne in an ascus

*Ascus* – the reproductive cell of the perfect stage of the ascomycete containing ascospores

*Basidiomycete* – fungus in which spores are borne on basidia.

*Basidiospore* – exospore on a special type of sporophore known as basidium.

*Basidium* – a special type of sporophore bearing exospore.

*Blastospore* – a thallospore that arises by budding from a parent cell and that may also throw out another bud or a mycelial filament, without becoming detached and without any period of latency Usually seen in yeasts

*Chlamydospore* – thallospore formed by the concentration of the protoplasm of a hypha within a swollen portion of the filament, the membrane of which becomes thickened. They are purely resting spores and are closely analogous in function to the spores of bacteria

*Conidium* – cell of irregular shape and size, borne free and originating asexually from the mycelial thread by a process of budding septation or abstriction. May be pedunculated or nonpedunculated, lateral or terminal

*Conidiophore* – a specialized hypha of sporophore bearing conidia.

*Ectothrix* – a fungus growing on the outside of the hair

*Endothrix* – a fungus growing within a hair

*Eumorphic* – well formed

*Fuseau* – a multiseptate, thick walled spore, also known as macroconidium.

*Hypha* – a chain of cylindric or club-shaped cells forming a filament (i.e. thread)

*Mycelium* – collection of hyphae.

*Oidium* – having conidia borne in chains.

*Perithecium* – a rounded, oval or pear shaped structure within which asci are borne

*Phialide* – a short spore bearing structure, also known as a sterigma

*Pleomorphism* – the occurrence of more than one independent stage or form in the life cycle of a species.

*Racquet cell* – club-shaped cell, the clubbed end of which being attached to a small end of an adjacent cell

*Sclerotium* – an aggregate of resting bodies of small size, composed of a hardened mass of hyphae, from which fruit bodies may develop

*Septate* – divided by a crosswall.

*Spiral or spiral hypha* – simple convoluted hypha that may take all the forms of a tendril—from a spirillum to a closely set coil.

*Sporangium* – a spore case.

*Sterigma* – a specialized hypha to which spores are attached.

*Zygospore* – a sexual type of spore produced by the fusion of two undifferentiated cells.

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*We wish to express our great appreciation to* NORMAN F. CONANT PH. D. *for his advice and criticism on the manuscript*

CHAPTER 51

# PHYSIOLOGY OF FUNGI GROWTH and REPRODUCTION

JACOB H SWARTZ
Boston

The fungi belong to the plant kingdom and are classified as thallophytes. Unlike the algae which obtain their nutrition from inorganic substances with the aid of chlorophyll and the sun s energy the fungi live on decayed organic matter

It is noteworthy that most fungi pathogenic to man belong within the Fungi Imperfecti, a group comprising those true fungi which lack a sexual stage to complete their life cycle Structurally the fungi are characterized by a vegetative body composed of filaments or hyphae and a reproductive organ made up of spores of various types and produced in various ways. When the environment is favourable for growth, reproduction will not occur If conditions are adverse, there is a tendency to spore formation. However before reproduction can occur growth must be sufficient to allow storage of the products necessary for the processes required for reproduction.

The fungi pathogenic to man may be classed as dermatophytes which are responsible for the superficial infections, and the deep mycoses which are the cause of visceral infections The former are usually found in relation to keratin, occurring in the stratum corneum, in the nail substance, in or on hairs and in the hair follicles. Some fungi have the ability to invade both the superficial and deep structures while others invade the deeper portions of the tissues and rarely invade the superficial structures.

#### WATER

The fungi require a relatively high humidity for optimal growth and reproduction. The water requirements, however, vary considerably according to the fungus species. Many of the lower fungi grow best when immersed in water, whereas others will form a thick hyphal mat on the surface of a liquid medium. Most fungi pathogenic to man grow best on semi-solid or solid media. Some fungi have the capacity to resist drying for a long period and will revive when moisture is added.

#### TEMPERATURE

The temperature requirements vary greatly with the species. Some fungi grow well only at body temperature while others will grow well at all temperatures between room temperature (20° C) and body temperature (37° C). Most pathogenic fungi grow well at room temperature. In general the reproductive forms can withstand higher and lower temperatures better than the vegetative structures; thin walled spores are less resistant than thick walled spores and sexual spores can withstand a higher range of temperature change than the asexual spores.

#### OXYGEN

Oxygen is required by the common pathogenic fungi for growth and reproduction. Actinomyces bovis, however, is an exception to this rule.

#### INORGANIC SALTS

Traces of potassium, magnesium, iron, and calcium are necessary to secure optimal growth and reproduction. Calcium is the least important. Phosphorus, sulfur, carbon and nitrogen are the non-metallic elements which are important.

#### CARBON

The carbohydrates and organic acids are the most important sources for carbon. Of these, glucose has the widest use. GODDARD found that certain fungi find it difficult to assimilate certain sugars. Trichophyton gypseum can utilize dextrose, fructose, maltose and galactose but not lactose, whereas Microsporum canis (lanosum) cannot assimilate galactose or lactose.

#### NITROGEN

The usual source of nitrogen in culture media is peptone. Keratin is the source of nitrogen in the skin. The manner in which the amino acids in keratin are utilized by the dermatophytes is still undetermined. No definite enzyme that actually hydrolyzes keratin has as yet been found. Most fungi require amino acids when grown on artificial media and a suitable mixture of amino acids is conducive for optimal growth and reproduction.

ROBBINS *et al.*, SCHOPFER and BLUMER, BURKEHOLDER and MOYER, MACKINNON and ARTAGAVEYTIA-ALLENDE, GEORG and others have shown that many dermatophytes actually have deficiencies for certain of the vitamins and amino acids and are stimulated by other growth factors present in natural products such as peptones, liver and yeast extracts.

#### VITAMIN AND OTHER NUTRITIONAL REQUIREMENTS

Some fungi require thiamine for optimal growth. GEORG has studied the vitamin and amino acid requirements of 11 strains of Trichophyton violaceum and found that 10 of 11 strains studied have in common a requirement for the pyrimidine portion of the thiamine molecule for good growth. Paraminobenzoic acid in large doses (78 to 300 micrograms) stimulates the growth of some fungi. BENHAM found that oxalacetate was active for pityrosporum ovale. LANGERON and MILOCHEVITCH have been able to induce the formation of spirals, microconidia and macroconidia in many strains of trichophyton which had not previously shown these structures on the usual Sabouraud's media, by growing these fungi on natural media of polysaccharide base which consisted of whole grains of wheat, barley, corn and oats. HAZEN demonstrated that yeast extract added to honey agar resulted in a marked increase in the vegetative growth of M. audouini and in the production of macroconidia.

#### HYDROGEN ION CONCENTRATION

Most fungi require a hydrogen ion concentration between 5 and 7 for optimal growth.

#### LIGHT

In the experience of most workers the growth of fungi is not in-

fluenced by light. One has to explain, however the fact that in some mycoses such as tinea versicolor the eruption is almost invariably confined to covered parts of the body Ultraviolet rays of special wave lengths do have an inhibiting but not lethal effect on certain fungi. Roentgen rays and radium have proved to have only *slight inhibiting* influence KELNER and others have been able by means of irradiation with X rays or in some cases with ultraviolet light to induce antibiotically active mutants in conidial suspension of antibiotically inactive actinomycetes.

## PIGMENT

As a result of their study on the production of pigment by certain fungi LEWIS and HOPPER concluded that the pigment is a metabolic product. Trichophyton rubrum and microsporum canis were able to synthesize pigment *in* the presence of certain monosaccharides with closely related structural formulas such as dextrose, levulose and mannose, and one disaccharide, manitol. Pigment was not produced in a medium in which the only sugars were galactose (a monosaccharide) or other disaccharides trisaccharides and polysaccharides. FOSTER stresses the role of minerals particularly iron, copper and manganese in the formation of pigment.

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# CHAPTER 52

# MYCOLOGICAL TECHNIQUE

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## INTRODUCTION

In the diagnosis of fungous infections direct examination of unstained material is a useful informative procedure for the clinical evaluation of a disease particularly when staining and cultural methods do not add appreciably to a specific diagnosis and effective therapy Such a simplification of mycological technique is rarely satisfactory The first step for an exact mycological diagnosis is the culture The macroscopic examination of a culture is never sufficient for arriving at a precise mycological diagnosis In many instances several laboratory procedures such as special culture media, slide cultures special stains fermentation, animal inoculation and immunological tests will become necessary to define the species

In the following pages an outline will be given of the laboratory procedures most of which are considered simple and essential.

## GENERAL RULES AND CONSIDERATIONS IN MYCOLOGICAL LABORATORY PROCEDURES

As a rule, pathogenic fungi require at least one week before good growth is noticed Sometimes even several weeks are necessary to attain full development. Therefore *any growth appearing within 48–72 hours particularly when pigment is produced should usually be considered a contaminant*

In most instance the contaminants are aspergilli, penicillia mucors, or fusariums. The latter has been confused with *Trichophyton rubrum* because of the reddish pigment formation Caution should be exercised in the handling of these *so-called contaminants since Coccidioides immitis can be mistaken for a contaminant* because of the quickly growing brownish fluffy growth In addition to *C immitis* *Nocardia asteroides* should be handled with the utmost care Spores may be inhaled easily and it is therefore, compulsory to wear a mask whenever working with these cultures.

Culture tubes should be labelled with the date of inoculation, source of material and the type of medium used and should be discarded only after 4 weeks.

Some of the dermatophytes (*T. violaceum* and *rubrum*, *Epidermophyton inguinale*) grow rather slowly. It is almost a general rule that the anthropophylic fungi (*Microsporum audouini*, *T. purpureum*, *Achorion schoenleini*) grow much more slowly than the zoophylic group (*M. lanosum*, *T. gypseum*) which may fully develop within 1–2 weeks. Most pigment producing fungi (*T. purpureum*, *T. sulfureum*, *T. violaceum*, *Epidermophyton inguinale*, *Sporotrichum schenki*) develop pigment rather slowly. *T. violaceum* may lose its pigment upon subculture.

*T. sulfureum* grows better at 37° C but the addition of thiamin facilitates growth at room temperature (CARNEY). Pasty greyish cultures are generally yeasts, most of which are saprophytes. However, when the same organism is isolated in several tubes and on repeated occasions, the pathogenicity of such a yeast must be considered. Slow growing fluffy cultures are generally dermatophytes (*T. purpureum*, *T. rubrum*, *E. inguinale*). The granular growth is indicative of abundant spore formation (*T. gypseum*, *N. asteroides*). Slow growing, waxy cultures are characteristic of *Achorion* and also of *T. violaceum* and *Sporotrichum schenki*.

These brief remarks indicate that it is not only essential to watch the rate of growth, but it is equally important to observe the surface structure and configuration (folds, furrows, ring formation) of a culture. The margin of a colony may be sharply defined (*Candida* group, *Torula histolytica*) or it may fade imperceptibly into the agar (*M. audouini*, *E. inguinale*). Some colonies are fluffy in the center and waxy at the periphery (*Blastomyces dermatitidis*).

Consideration should also be given to the geographical distribution of the fungus flora. Besides the cosmopolitan fungi, there are species which are known to exist in certain countries or among certain races: *Microsporum ferrugineum* in China, Japan; *Cladosporium wernecki* in Central and South America, *Glenospora albiciscans* in Southeast Asia, *Actinomyces keratolyticus* in India, *Paracoccidioides brasiliensis* in South America, *Trichosporon hortai* in South America, Indo-China, Java and Borneo; *Coccidioides immitis* in the southwest United States and Argentina, *Madurella* mainly in the subtropic and tropics.

A single culture is never satisfactory and it is highly recommended that repeated cultures (at least three) should be made when the clinical picture indicates a mycological investigation. Special attention must be paid to previously treated lesions. Treatment should naturally be suspended in such instances and a period of several days has to elapse before a culture can be made. WEIDMAN had some success in applying wet glucose dressings to lesions, particularly between the toes for 48 hours or more before taking additional scrapings.

## COLLECTION AND CULTURING OF MATERIAL FROM SKIN, HAIR AND NAILS

It is not necessary to swab the parts to be examined with 70% alcohol, but

it is helpful. Contamination of subsequent cultures may thus be reduced but not entirely avoided. Elimination of contaminants particularly of bacteria, can be achieved by special media which will be discussed later. The most frequent errors are the paucity of the material collected and the practice of preparing one single culture. The following rules in collecting and culturing material should be kept in mind.

## SUPERFICIAL FUNGOUS INFECTIONS OF THE SKIN

*Tinea corporis.* The most promising way to obtain fungous material is to scrape the border of a suspected mycotic skin lesion. In palmar and plantar lesions due to *T. purpureum* infection, fungi are generally in the deeper strata of the horny layer. Vesicles on feet and hands should be examined *in toto*. The roofs of these vesicles harbour rich fungous material (generally *T. gypseum*)



691. Malassezia furfur: curved and straight mycelia and clusters of spores in scrapings from the skin.

(Hotchkiss–McManus Stain, ×700)



692. Candida albicans: scrapings from the skin illustrating long straight and curved mycelia with budding and non-budding yeast cells.

(Hotchkiss–McManus Stain, ×700)

and it is self-evident that the underside of the vesicles should be planted in a culture tube. The removal of the vesicle is easily accomplished by snipping off the roof of the vesicle with small curved scissors after previously transfixing it with a needle. The material can be immediately planted on Sabouraud's glucose medium or can be preserved for several months wrapped in black paper. The black paper background is rather advantageous for picking out the right material.

Several samples from different sites of a tinea are recommended. The centre of such lesions is generally free of fungi except in *Tinea imbricata* where fungi are abundant wherever scraping is done. This technique applies not only to the cosmopolitan superficial mycoses caused by *Trichophyton*, *Microsporum*, *Epidermophyton* and *Achorion*, but also to the rarer

superficial dischromic tropical mycoses (Hody potsy chimberé *Tinea albigena* and *Tinea nigra*)

*Tinea versicolor erythrasma piedra* In the scrapings from lesions of *Tinea versicolor* and erythrasma, fungi are found in large numbers. While the fluorescence of lesions of *Tinea versicolor* is, at times of some diagnostic help the ultimate diagnosis rests with the microscopic examination. The fungous elements of *Tinea versicolor* can be demonstrated easily with a low power KOH preparation, but the causative fungus of erythrasma *Microsporon minutissimum* can be demonstrated only with oil immersion and still more with appropriate staining (methylene blue or lactophenol cotton blue). Culturing of the latter fungus has been reported only on special media but it is not a routine procedure because it does not grow on Sabouraud's medium. The presence of stony hard nodules in the bearded region or hair is suspicious of piedra. These nodules are easily seen and, at times removed only with difficulty Fungous elements are clearly demonstrated in potassium hydroxide preparations and these fungi can be cultured

*Onychomycosis* In nail scrapings fungi are generally in the deeper strata and, therefore, the superficial scrapings should not be saved. An exception is onychomycosis due to *T gypseum* in which instance even the most superficial layers harbour fungi. A dental burr or a nail file is a great help in collecting nail material.

*Tinea capitis Sycosis parasitaria and Trichomycosis axillaris* It is preferable to collect fluorescent hair (see section on fluorescence) for microscopic examination and for culture. However it should be kept in mind that hair infected with *Trichophyton* and *Achorion* does not fluoresce. Therefore suspected broken hair from the scalp or bearded region should be carefully extracted from the follicles with the help of a hand lens and preserved for mycological investigations Scutula (favus) almost always yields positive results. At times, however favus also resembles a dry flaky seborrhoea of the scalp or a follicular pustule. These are exceptions but should not be disregarded as a possible source of fungous material. Fungous elements in trichomycosis axillaris can be demonstrated easily in the beaded hair of the axillae. This fungus (*Actinomyces tenuis*) can be demonstrated only with high power magnification.

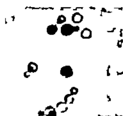
*Infections due to Candida* In suspected paronychia due to *Candida* material may be collected from the discoloured lateral nail borders or from scrapings from the paronychial tissue. At times a droplet of pus can be squeezed out, which could be of diagnostic value. Material can be similarly collected from the angles of the mouth (perlèche) or from an intertriginous or other cutaneous surface (Erosio interdigitalis blastomycetica) vaginal scrapings may also yield this organism.

## DEEP (SYSTEMIC) MYCOSES

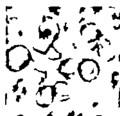
Material from the deep mycoses is recovered either from the pus of draining

sinuses or abscesses but fungi are more likely to be found in unopened and uncontaminated lesions. For culturing unopened lesions are particularly preferred. This applies especially to sporotrichosis blastomycosis chromoblastomycosis coccidioidomycosis South American blastomycosis histoplasmosis madura mycosis and torulosis. When granules are recovered from actinomycotic sinuses cultures may be more successful. If granules are not available, it is recommended to wait 1–2 days or to irrigate the sinuses with sterile saline solution. A practical procedure is to cover the sinuses with dry sterile gauze pads for 12-24 hours and thus the granules may be caught between the meshes. These granules should be placed on a slide, covered with a cover slip and examined in 10–20 % KOH solution. For finer details Gram s or acid fast stain is advised At times the granules are encrusted with lime salts in which case a treatment with a 2 hydrochloric acid solution is necessary in order to visualize the structure of the granules.

Except in sporotrichosis in all deep mycoses the respective fungi can be



693 Blastomyces dermatitides from tissue section of infected mouse showing budding and non budding yeast cells with a thick wall. Similar forms are found in material originating from human blastomycosis (Hotchkiss–McManus Stain 700)



694 Chromoblastomycosis Tissue section stained with Hotchkiss McManus stain This illustrates some forms grouped in clusters with septation, which are also found in pus and are dark brown

readily demonstrated in direct KOH preparations. The parasitic form of sporotrichosis can be seen but rarely in purulent material. Scrapings and biopsied tissue from suspected rhinosporidiosis should be examined directly in KOH solution or fixed in Bouin s solution for histological examination Up to the present culture media are not available for the culturing of *Rhinosporidium seeberi* which is considered the causative organism.

*Material from Spinal Fluid* In meningism of undetermined aetiology particularly when associated with protracted course of fe attention should be paid to the presence of Torula histolytica in the spinal fluid These organisms can be demonstrated easily in making smears mixed with India k (WEIDMAN) The technique is similar to blood smears The following pathogenic organisms are rarely isolated from the spinal fluid *Histoplasma capsulatum* *Nocardia asteroides* and *Candida albicans*

*Material from Sputum.* Sputum may harbour many saprophytic candida and actinomyces species, even after rinsing the oral cavity several times and after brushing the teeth. Great care must be taken that only sputum from the lung and not saliva or nasopharyngeal secretion be examined. The best method is to collect material on sterile Petri dishes which should be sent to the laboratory immediately. The primary isolation of pathogenic fungi on appropriate media should be attempted, of course. This is preferable because most clinical specimens are rendered useless for culturing after 24 hours. This should always precede the direct examination in a 10 % KOH solution. The following pathogens are significant in case they are repeatedly recovered in the sputum or from material collected through the bronchoscope: *Candida albicans*, *Geotrichum*, *Blastomyces dermatitidis*, *Blastomyces brasiliensis*, *Coccidioides immitis*, *Sporotrichum schenckii*, *Nocardia asteroides* and, less frequently *Actinomyces bovis*, *Histoplasma capsulatum*. There are several reports of mucormycosis, penicilliosis and aspergillosis of the lung but, since these organisms are so frequently present as contaminants, it is rather difficult to establish an aetiological relationship, even if they are repeatedly found and isolated from sputa.

*Urine.* Pathogenic fungi are seldom isolated from the urine. The most frequent aetiological organism of primary cystitis is *Candida albicans*, which frequently occurs in diabetics. OTA and MASUDA, however, found a yeast organism which does not belong to the *Candida* group in patients with cystitis. In systemic blastomycosis and cryptococcosis the respective organisms may be isolated from the urine as well.

*Blood.* Blood cultures are not performed routinely in the diagnosis of fungous infections. Therefore the diagnosis of these diseases does not depend on blood cultures. It is significant, however, that *Histoplasma capsulatum* has been isolated from the blood (KUNSTADTER). It is of equal interest to note that *Candida parakrusei* has also been isolated from the blood of drug addicts suffering from endocarditis (WICKLER *et al.*). This organism is not pathogenic for laboratory animals, which is indicative that no conclusion can be drawn from a negative animal experiment with respect to a potential pathogen in humans. Attention should be paid to the possibility, although it is a rarity, that actinomycetes can be the causative agents of endocarditis and that this organism has also been isolated from the blood (BLEVINS *et al.*).

*Faeces.* With the exception of *Actinomyces* which has been isolated from the vermiform appendix and *Candida albicans* which has been found in the faeces of advanced cases of generalized moniliasis, little significance should be paid to isolates from the intestinal canal. *Histoplasma capsulatum* has rarely been found in faeces. However, yeasts and several yeast like organisms (including *Candida albicans*) constitute the normal intestinal flora and, therefore, a multitude of organisms may be isolated, the pathogenicity of which remains unproven or doubtful in most instances (SCHNOOR).

## DIRECT MICROSCOPIC EXAMINATION OF MATERIALS

The material collected from hair, skin, nail scrapings, pus, sputum, granules etc. should be placed on a slide, a few drops of 10–20 % KOH added and then covered with a coverslip. It is advisable to warm the slide and wait 30–60 minutes for clearing before a microscopic examination is made. WILLIAMS suggested the use of glycerin in addition to potassium hydroxide in treating skin scrapings, hair or nail. Such a preparation is particularly

useful for further examination because mycological structures can be preserved in this way for several months. LEWIS and HOPPER recommend an aqueous solution containing 5 potassium hydroxide and 25 glycerin. This may serve for a semipermanent preparation in which little or no crystallization occurs. Equally good results are obtained in using Aman's chloral-lactophenol (2 parts chloralhydrate, 1 part phenol 1 part lactic acid) or lactophenol (1 part phenol 2 parts lactic acid, 2 parts glycerin 1 part distilled water)

Just as it is unsatisfactory to prepare only one culture, it is equally unreliable to draw a conclusion from a single preparation. At least 3 slides should be examined. The thinner the preparation the better is the visualization. The low power magnification is most suitable for finding the desirable place for examination. While this magnification is sufficient for the advanced mycologist, beginners should make use of high dry power objectives. The diaphragm should only permit limited illumination, since too strong a light is rather disturbing in tracing fungous elements

It is impossible to draw any conclusion from positive mycological findings



695 Coccidioides immitis spherule in pus (KOH preparation, 700)



696 Paracoccidioides brasiliensis culture mount in lactophenol cotton blue ( 1000), showing large parent cell with numerous buds as well as single cells without budding and with single buds.

as to the nature of the fungus because microsporons trichophytons epidermophytons and achorions produce similar mycelia in the skin or nails. However some conclusion can be drawn from the location of the spores in the hair (ecto- or endo thrix) or from the size arrangement and shape of the spores. The parasites of the genus *Achorion* invade the hairshaft and form chains of round or rectangular spores with occasional air bubbles between the spores. Microsporons form an irregular mosaic pattern of small spores around the hairshaft. Trichophytons may either form parallel chains of equal sized, large, rounded spores inside the hair (endothrix) or the hairshaft may be covered with regularly arranged longitudinal chains of either small spores (microid ectothrix) or large spores (macroid ectothrix)

At times doubt arises whether or not certain structures are mycelia or yeast

bodies. Moderate pressure with a pencil on the coverslip is a procedure for ascertaining the fungous nature of such structures. On pressure air bubbles fat globules or potassium hydroxide crystals change their shape. Keratohyalin granules may also simulate spores particularly in scrapings from the palms and soles. However the intracellular localization of these amorphous granules can be easily demonstrated by manipulating the fine adjustment of the microscope while examining the field.

The so-called and often disputed *mosaic fungus*" which appears microscopically as a network of refractile debris has been misinterpreted at times as a pathogenic fungus. DOWDING gave some evidence that the "mosaic fungus" is neither cholesterol nor a living fungus nor artefacts of the mounting medium but is probably comprised of disorganized hyphae of fungous elements.

## STAINING AND MOUNTING METHODS

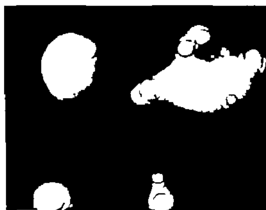
Since potassium or sodium hydroxide dissolves not only keratinic structures but, also volutin (which is one of the main constituents of the mycelial and spore wall) staining may become a necessity for the preservation of material. The first and most important step is the defatting of the skin, nails or hair After having teased the material with two needles, a liberal amount of Carnoy s liquid (10 parts glacial acetic acid, 30 parts chloroform 60 parts absolute alcohol) should be poured on the slides without overflooding the slide and losing the material. This may be prevented by pasting the scales or hair to the slides with raw egg white. After 5–10 minutes another slide should be placed on the slide with the material and gently rubbed. The slides are then separated. This divides the material between the two slides. Then they are dried in the air not over a gas burner because of the chloroform content.

The dried preparation can be stained for 5–10 minutes with methylene blue or Giemsa s stain. This is followed by washing in tap water for 1–2 minutes and followed by decolorizing with a 1 % aqueous solution of acetic acid. This must be performed carefully and not longer than 1–2 minutes because longer exposure decolorizes all structures. Then the preparation is washed for 1–2 minutes in water followed by 5 minutes in absolute alcohol clearing for 5 minutes in xylol, and mounting the specimen in Canada balsam or clarite Several other methods are also available, requiring more time without giving greater advantage. A simple and quick procedure for staining larger scales or hair is the following the material is defatted with an equal mixture of alcohol-ether in a watch glass and then dried. This is followed by staining 5–10 minutes with a concentrated Giemsa solution, rinsing with tap water and decolorizing for 5–15 minutes with a ½ % tannic acid solution or alcohol After this the preparation is washed in tap water cleared in xylol and mounted in Canada balsam or clarite.

KLIGMAN and MESCON applied the Hotchkiss-McManus stain not only

for the demonstration of fungi in tissue sections but also for the staining of skin scrapings and culture material. Except for *Actinomyces bovis* and *Nocardia asteroides* this stain is highly recommended and possibly superior to the results obtained with other staining methods. This can be confirmed, but because of the amount of time required, it is not advantageous as an office procedure. The method is as follows

Tissues have to be fixed in either 4 formaldehyde or Rossman s fixative embedded and sectioned. After deparaffinizing and dehydrating the sections wash in distilled water Then the material should be immersed for 5 minutes in a 1 ° periodic acid solution and afterwards washed for 10–15 minutes in running water Then the sections (or fungous material) have to be transferred directly to two changes of either of the following two solutions for 5 minutes a) 5 ml of 10 potassium metabisulphite 5 ml of 1 N



697 Cryptococcus hominis culture mount treated with India ink illustrating the large gelatinous capsule and budding (× 700).

HCl 100 ml distilled water or b) 5 ml thionyl chloride, 100 ml distilled water After washing in running tap water for 10 minutes the material (section or fungus culture) should be counterstained with light green dehydrated, cleared and mounted.

The Schiff reagent is prepared by either of the following methods a) Dissol 0.5 g basic fuchsin by pouring o r 100 ml of boiling distilled water then cool to 50° C, filter and add 10 ml 1 N hydrochloric acid and 0 5 g anhydrous potassium metabisulphite to the filtrate Allow the solution stand in the dark overnight. It should become colourless or pale straw colour It not completely decolorized, add 0.5 g charcoal, shake thoroughly and filter immediatel This solution will keep for several weeks in a tightly stoppered bottle b) Dissol 0.5 g basic fuchsin by pouring over it 100 ml of boiling distilled water c ol to 50° C, filter and dd lowly 5–8 ml thionyl chloride and clear with charcoal

AREA LEAO recommends the following simplified technique

1 Place the material to be examined on a clean slide, or into a small watch-glass, and pour over it a freshly prepared mixture of 9 parts of hydrogen peroxide, 12 volumes and 1 part ammonia.

2. Heat mildly over a flame until steaming or leave the material for several hours exposed to laboratory temperature until bleaching of the material takes place. This can be seen easily under the microscope.

3. After bleaching, the mixture of hydrogen peroxide-ammonia should be poured off. The slide should be repeatedly dipped in absolute alcohol and, after clearing in xylol, the specimen can be mounted in Canada balsam.

Lactophenol may also be used for mounting in which case the cover glass edges should be varnished. This method furnishes preparations of great neatness, produces a fine differentiation of the fungus and preserves material without alteration of the structure of hairs.

## CULTURE MEDIA

With the exception of *Rhinosporidium* and *Malassezia furfur* most pathogenic fungi can be grown on either solid or liquid media. As a routine procedure, the most suitable is Sabouraud's 4 % glucose agar which can be substituted for primary cultures with a medium containing 2 % glucose and 1 % peptone. The pH should be adjusted to 5.6 Most dermatophytes and nocardia will grow on this medium at room temperature. Except for hair skin, and nail scrapings only fresh material is suitable for culturing The material should be placed in the center of the tube, using a platinum loop Flaming of the cotton plug and the mouth of the tube is not absolutely necessary Care should be taken, however that additional contaminants should not be introduced by careless handling of the cotton plug

The following is the composition of Sabouraud's glucose or maltose agar

| | |
|---|---|
| Dextrose (or maltose) | 40 g |
| Agar | 18–20 g |
| Peptone | 10 g |
| Distilled water | 1000 ml |

This mixture should be melted in the autoclave, filtered through cotton gauze and added to culture tubes. Autoclave at 15 lbs for 15 minutes. Excessive autoclaving produces caramelization which makes the medium unsuitable.

A simple office procedure for culturing fungi has been described by PLUNKETT and WILSON. Instead of the usual cotton-stoppered test tubes small square bottles with plastic screw caps are recommended. The screw cap closure prevents to a certain extent, drying of the medium. These small bottles also require less space than test tubes. The authors have also suggested a modification of Sabouraud s agar which consists of 1 per cent peptone, 2 per cent agar and 4 per cent glucose in tap water Adjustment in pH is necessary only when the water is alkaline Care should be taken that after inoculating the bottles, the screw caps should not be closed too tightly

In order to induce intense spore formation, BENHAM has recommended a blood agar base (B.A.B.) medium, which has the following composition: Infusion from beef heart 500 grams. Bacto tryptose 10 grams. Sod. chloride 5 grams. Bacto agar 15 grams. This medium is particularly useful to produce macroconidia in T. purpureum.

*Blood agar* tubes are recommended for the study of dimorphic fungi: *Histoplasma capsulatum*, *Blastomyces dermatitidis* and *Paracoccidioides brasiliensis*. The tubes should be incubated at 37° C. Tubes in which *Histoplasma capsulatum* is expected to grow should be sealed.

*Corn meal agar* is used for the differentiation of the yeasts and cryptococci from the pathogenic species *Candida (monilia) albicans*. *Candida albicans* is the only species which produces chlamydospores on this medium. Furthermore a deep stab with a needle containing the cultural growth produces a picture of an inverted pine tree.

The composition of corn meal agar is the following:

| | |
|---|---|
| Corn meal | 40 g |
| Distilled $H_2O$ | 1000 ml |
| Agar | 20 g |

Simmer corn meal and water for one hour, then filter through gauze. Before adding the agar, adjust the volume to 1000 ml. After melting the agar in the autoclave, the mixture should be filtered through two layers of cotton and gauze. The flask containing the agar should be placed over a steam bath, otherwise the agar will soon harden. Tube and autoclave at 15 lbs pressure for 15 minutes.

CHAPMAN recommends the following medium for the isolation and differentiation of monilia:

| | |
|---|---|
| Neopeptone | 10 g |
| Maltose | 40 g |
| Agar | 15 g |
| Tergitol 7 (Carbide and Carbon Chem. Co.) | 0.10 ml |
| Bromcresol purple 1.0 | 2.5 ml |
| Water | 1000 ml |



698. Actinomyces granule from tissue section stained with haematoxylin and eosin. The shape and structure of granules originating from draining sinuses are similar (× 400)

Adjust the pH to 5 6 and sterilize for 10 minutes at 14 – 1 lb.

When cool and ready to pour add

| | |
|---|---|
| Potassium tellurite | 0.3 ml |
| 2, 3 5 triphenyltetrazolium chloride 1 % | 3.0 ml |

*Candida albicans* produces "off white" colonies about 4 mm in diameter depending on the density of the growth They are circular smooth entire, and convex to pulvinate.

LUCILLE GEORG and AJELLO suggest the addition of 0 1 mg actidione/ml of basal agar for the isolation of *Coccidioides immitis* particularly from the air The basal agar consists of Sabouraud's dextrose agar fortified with 20 units/ml penicillin and 40 units/ml streptomycin. REISS and CAROLINE found an increase of pigment formation of *T gypseum* and a decrease of pigment production of *T purpureum* on Sabouraud's glucose agar to which trimeton maleate is added in 0 06 molar concentration. This phenomenon may serve as a simple guide to differentiate the two species.

BOCOBO and BENHAM found a 2 per cent dextrose corn meal agar useful for the cultural differentiation of T gypseum from T purpureum. On this medium only T purpureum produces pigment. Similar results have been obtained by CLAIRE TASCHDJIAN using a 2 per cent dextrose—rice infusion agar (20 g rice to 1000 ml water).

DE LAMATER recommends a dextrose nutrient agar to which 25 units per ml of penicillin and streptomycin have been added for the primary isolation of *Histoplasma Coccidioides* and *Blastomyces*

This dextrose nutrient agar consists of the following

| | |
|---|---|
| Distilled water | 1000 ml |
| Peptone | 10 g |
| Sodium chloride | 5 g |
| Beef extract | 3 g |
| Dextrose | 5 g |
| Agar | 15 g |
| *N*/10 Sodium hydroxide | 1 ml |

Tube and sterilize

For the primary isolation of *Nocardia*, but particularly of *Actinomyces* either *thioglycollate broth* veal infusion agar, or the Norris medium is recommended.

*Brewer's thioglycollate medium*

| | |
|---|---|
| Pork infusion solids | 1 g |
| Peptone (thio) | 1 g |
| Sodium chloride | 0.5 g |
| Sodium thioglycollate | 0.1 g |
| Agar agar | 0.05 g |
| Distilled water to make a final volume of | 1000 ml. |

*Norris Medium*

| | |
|---|---|
| Soluble starch | 2.0 g |
| Dipotassium hydrogen phosphate | 0.2 g |
| Calcium chloride | 0.05 g |
| Ferric chloride | 0.01 g |
| Sodium nitrate | 0.06 g |
| Asparagine | 0.05 g |
| Agar agar | 20.0 g |
| Distilled water to make a final volume of | 1000 ml |

As already mentioned culture tubes should be held for at least three four weeks. As a rule, pathogenic fungi grow much slower than fungous contam



699 Microsporon infected hair showing small spores in mosaic-like pattern rranged around the hair i sheathe-like manner (KOH mount 700).

inants or bacteria Both cause great difficulty not only because their growth overshadows the growth of pathogenic fungi, but also may inhibit the growth of pathogenic fungi Saprophytic fungi are rather difficult to suppress on the routine media An appreciable advance was made with *Littman's oxgall agar* which not only restricts the growth of both Gram-negative and Gram-positive bacteria, but also causes saprophytic and pathogenic fungi to grow as small well separated, non-spreading colonies

## CONSERVATION OF CULTURES

Most cultures become dehydrated when maintained at room temperature Therefore transfers have to be made at 6–8 week intervals, particularly when fungi are grown on rich nutrient media. Otherwise some of the dermatophytes undergo a degeneration called pleomorphism. Such strains lose their distinguishing characteristics and are transformed into a woolly sterile mycelium

*Muskatblit* uses large culture tubes which contain 60 ml of conservation agar. Such cultures have to be subcultured only every 6 months. Lyophilization and cold storage are not suitable for most anthrophyllic fungi. SABOURAUD recommended a conservation agar which has only a limited value since many strains do not develop because of the stunted growth on the conservation medium. The formula of this medium is the following

| | |
|---|---|
| Agar | 18 g |
| Peptone | 30 g |
| Distilled water | 1000 ml |

AJELLO GRANT and GUTZKE made a valuable contribution in the preservation of stock cultures. After the fungi have attained a colony size of 1 cm in diameter heavy mineral oil (autoclaved for 30 minutes at 15 lbs pressure) is added in quantities sufficient to cover completely both the fungus growth and the surface of the agar slope. The tubes can be stored at room temperature. Cultures remain viable for 19–21 months. The usefulness of this method has been confirmed in our laboratory

## PRESERVATION OF CULTURES

In order to keep a display of morphological characteristics of fungi, it is desirable to preserve a collection of representative fungi for an indefinite period. After the colony has reached full development, LEWIS and HOPPER recommend moistening the cotton pledgets with 10 drops of a 40 % solution of formaldehyde and replacing them in the test tubes. After 24 hours, the pledget is trimmed off and the test tube is sealed with paraffin to make it air-tight. We have used a similar method for the preservation of giant cultures. A sterile filter paper is saturated with 40 % formalin and placed under the lid of the Petri dish. After 24 hours the paper is removed and the dishes are sealed either with paraffin or scotch tape. It is obvious that such strains lose their microscopic characteristics.

## CULTURE MOUNT

The simplest approach to the examination of the microscopic features of a fully developed colony is to take a small amount of growth from the center of a colony where characteristic generative structures are more likely to be present than on the periphery Such a mount can be examined in a drop of 10 aqueous KOH solution but it is preferable to stain with Amman's lactophenol cotton blue, the composition of which is the following

| | |
|---|---|
| Phenol crystals | 20 g |
| Lactic acid syrup | 20 g |
| Glycerol | 40 g |
| Water | 20 ml |

These substances are dissolved together with gentle warming then 0.05 g of cotton blue is added. Yeasts can be stained with Gram's Lugol solution.

These procedures as a rule disturb the spore mycelium relationship and give information only of the gross characteristics of a fungus. The method of BENEDEK for studying a colony grown in a test tube directly under the microscope has certain advantages but at times the density of the growth does not permit a clear visualization of characteristics and furthermore, fructification organs may be absent on the periphery



700 Trichophyton (Endothrix) infected hair showing large arthrospores arranged in parallel chains, situated inside the hair (KOH mount × 700).

When various developmental stages such as the structure of the thallus or spore formation have to be studied hanging drop or slide culture preparations must be prepared. The latter procedure serves not only for the study of the various developmental phases of a strain but also may be used for the primary isolation and quick identification of fungi (RAUBITSCHEK and SAGHER LA TOUCHE, KLIGMAN and REBELL, ZIMERINOV and RAFALOVICH)

*Hanging Drop Preparation (van Tieghem cell)* This procedure is one of the oldest ways to study fructification organs. A few drops of water are placed in the center of a hollow or regular slide which is surrounded by a glass ring cemented to the slide.

Another drop of sterile water or preferably nutrient glucose or maltose is placed on top of a sterile cover glass which should be large enough to cover the ring Then a tiny bit of inoculum is placed in the centre of the drop the slide is quickly and carefully inverted and pressed on the top of the ring which is coated with sterile petrolatum. Such a moist chamber may be examined microscopically at suitable intervals and the development of the

fungus growth watched. The composition of nutrient glucose or maltose is as follows:

| | |
|---|---|
| Glucose (or maltose) | 4 g |
| Peptone | 1 g |
| Distilled water | 100 ml |

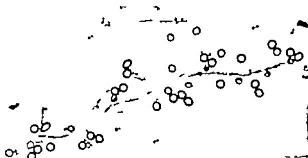
*Henrici Culture Chamber Method.* A piece of blotting paper or several layers of filter paper are placed in the bottom of a Petri dish and sterilized in an autoclave. Before using the dish, the paper is moistened with sterile water Then, several cover glasses are cleaned, placed in alcohol, sterilized by flaming and placed on the surface of the paper A tube of agar is melted in a water bath and cooled to a temperature not lower than 43 and not higher than 46 C. (Such tubes can be held in the hands without giving the sensation of unpleasant heat). Then the liquified agar is inoculated liberally with the mold to be studied. With a wire loop one or two loopfuls of the agar are thinly spread over the flamed cover glasses. It is of paramount importance to maintain a constant moisture in the Petri dish by wetting the blotting paper from time to time with sterile water When sufficient growth has taken place, a cover glass may be removed with a sterile forceps at desirable intervals. Such coverslip cultures may be studied immediately by placing the preparation on a slide moistened with a drop of water

Permanent preparations may be made in the following way Place a few drops of 95 % alcohol on one of the coverslips. Drain off the excess alcohol by placing the coverslip on a gently heated surface (radiator) After placing a drop of lactophenol cotton blue on the cover glass, it is inverted on a slide for a permanent mount. After 1–2 hours the excess lactophenol should be removed and the preparation may be sealed with any available cement or varnish.

*Huber's Plastic Mount* This procedure combines staining preservation and sealing and consists of a mixture of polyvinyl (P V.A.) lactic, acid phenol and cotton blue. Mounts prepared from P V.A. are resistant to ether xylol and acetone. The stock solution of P V.A. is prepared according to Downs. Fifteen grams of P V A powder (grade R.H. 349) are added to 100 ml cold water The mixture is then stirred and heated in a water bath at a temperature of about 80 C. The heating process is continued until the solution has the consistency of thick molasses. If undissolved particles remain, the solution is filtered through two layers of cheese cloth The P V.A. lactophenol mounting solution is prepared by combining P V.A stock solution 56 phenol 22 and lactic acid 22 % by volume to which 0.05 % cotton blue is added. In mixing, the lactic acid must be added first to the P V.A. solution before the phenol is added. Otherwise the P V.A. will change to a soft sticky mass. It is advisable to leave the fungous material in contact with the mounting medium for 30–60 seconds before the coverslip

is placed over the preparation. Thin skin scales or hair infected with fungi may also be mounted with this method

It should be mentioned that liquid media are preferable to the agar because the agar takes up the dyes rather intensely and this may interfere with the clarity of microscopic interpretation.



701 Candida albicans culture mount from corn meal agar illustrating numerous chlamydospores (Hotchkiss McManus Stain, × 700).

## FUSION OF MYCELIUM

The method described by DAVIDSON is recommended for the identification of an unknown species. This procedure is based on the well known fact that only mycelia of the same species will fuse when mixed together. The mycelia of two strains of *T gypseum* will fuse, while *M audouini* and *T gypseum* will not show this phenomenon. Similarly *M audouini* will not fuse with mycelia of *M lanosum* The method is of academic interest, but it is not recommended for practical purposes.

## GIANT COLONIES

Although most pathogenic fungi develop sufficient morphological features in test tubes more satisfactory information is obtained from cultures grown either on Petri dishes or in Erlenmeyer or Roux flasks. The inoculation is done by removing a tiny particle from the stock culture with a hooked or straight wire and placing it gently in the center of the medium. Flasks are preferable because Petri dishes dry out too soon, at times although Petri dishes are more suitable for photographic purposes Giant cultures are recommended not only for the study of dermatophytes but also of yeasts, some of which have a characteristic texture and form. Giant colonies should be allowed to grow for 4–6 weeks.

## FERMENTATION

The fermentation of sugar is an aid in identifying species of *Candida* although certain morphological characteristics have also been described (REISS) It should

be emphasized, however that the fermentation characteristics are not constant (BENHAM) and may vary according to the age of a culture and the medium on which a yeast is grown

LANGERON and GUERRA and MARTIN and his associates have recommended a paraffin jelly seal for studying gas production in fermentations. Much simpler and quite satisfactory are the Durham tubes containing freshly prepared 1 % peptone, 3 % glucose or maltose, sucrose and lactose in 30 ml of distilled water One ml of standard bromthymol blue solution should be added to 400 ml of medium before autoclaving The tubes are inoculated with 0 1 ml of an emulsion of one week old cultures and should be kept at room temperature (25° C). In order to avoid a mechanical blocking at the base of the gas trap it is recommended that the cultures be shaken gently after 24–48 hours. The tubes should be examined after the third or fourth day but it is advisable to keep the tubes up to 20 days. (*C guilliermondi* may f rment glucose and *C parapsilosis* may ferment sucrose only after 20 days).

MARTIN found the following fermentation reactions:

| | C. albicans | C. tropicales | C. pseudo-tropicales | C. krusei | C. para-krusei | C. stellatoidea | C. guilliermondi |
|---|---|---|---|---|---|---|---|
| Glucose | AG | AG | AG | AC | AG | AG | — |
| Maltose | AG | AG | — | — | — | AG | — |
| Sucrose | A | AG | — | — | — | — | — |
| Lactose | — | — | AG | — | — | — | — |

Occasionally acid only

According to LANGERON and GUERRA, gas is produced in glucose and sucrose when cultured at 25 °C and held for 20 days. A = acid, G = gas.

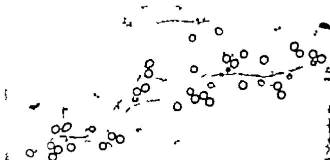
It is of interest to note that many strains of *Cryptococcus hominis* ferment only glucose with acid formation. The fermentation properties of this fungus, however should not be decisive in determining the pathogenicity of a strain.

## FLUORESCENCE OF CULTURES

The contribution of MARGAROT and DEVEZE that hairs infected with microsporums display a greenish fluorescence under filtered ultraviolet light has greatly facilitated clinical and epidemiological studies. The application of the same phenomenon, however does not have a similar significance in relation to cultural studies. In our laboratory comparative investigations have been made between the fluorescence of cultures on rice, maltose and glucose agar and corn meal mediums and it can be stated that fluorescence varies markedly not only with the medium, but also with the age of the culture. Fungi which show fluorescence on glucose medium (*M lanosum T gypseum T purpureum T tonsurans*) lose this characteristic with the aging of the culture and fluorescence is hardly perceptible after about two weeks growth. Our preliminary studies have shown that there is some variation in

is placed over the preparation. Thin skin scales or hair infected with fungi may also be mounted with this method.

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*The photographs included in this chapter are from the Skin and Cancer Unit of the University Hospital, New York University Bellevue Medical Center. I wish to express my sincere thanks to Mrs Claire Tarchdjian, Assistant in Clinical Dermatology (Mycology) and to Mrs Eleanor Morland, Photographer.*

CHAPTER 53

# EXPERIMENTAL MYCOTIC INFECTIONS IN LABORATORY ANIMALS

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Experimental mycology has many features in common with other branches of microbiology *In mycology in order to prove the pathogenicity of an isolated fungus it is important to fulfil* KOCH s *postulates* The applicability of this criterion, however is fraught with difficulties. Not only is it impossible to infect animals with common human pathogens such as the anthropophylic microsporons but the transmission to animals of some trichophytons and all epiderm phytons has also been unsuccessful However animal experimentation with representative strains of the zoophylic group of the dermatophytes and with fungi causing deep mycoses has fulfilled the postulates of KOCH and has been of fundamental importance in the understanding and appreciation of immunological phenomena. Attention should be called to the variation in susceptibility of different animals to various species The guinea pig is the most susceptible animal for producing a model infection with *Trichophyton gypseum* There is a noticeable difference however in the course of the infecti n in rabbits and cats (DE LAMATER and BENHAM) The white rat is susceptible to experimental spor otrichosis and the white mouse t blastomycosis to enumerate a few examples.

Besides producing model infections in animals experimental mycology has several other purposes

1 Animal inoculations may be of diagnostic importance in instances where either the macrosc pic or the microscopic features of a culture are diagnostic, as in *Coccidioides immitis*

2 To obtain the tissue phase f certain mycologically well-defined genera (*Sporotrichum Histoplasma*) which othe wise require special media (*Sporotrichum*) or cannot be pr duced at all on culture media (*Histoplasma capsulatum*) animal inoculations are helpful (Fig 702).

3 In the absence r failure of a cultu e infected material hair scales pu spinal fluid may be used to pr duce diseases in animal

4 To determine the hair-spore relationship (ecto- or endothrix) of a newly isolated and unknown dermatophyte animal experiments are desirable.

5 Finally animal passages generally increase the pathogenicity of some fungi (*Achorion canis* e g becomes more virulent for dogs after a mouse passage etc.)



702. Experimental histoplasmosis in hamster showing tissue phase of H capsulatum. Giemsa stain of impression smear of liver
(*Charles W Emmons*)

## GENERAL RULES AND CONSIDERATIONS IN EXPERIMENTAL MYCOLOGY IN SMALL LABORATORY ANIMALS

In order to produce optimal experimental fungous infections freshly or recently isolated cultures should be used. Fungi belonging to the systemic mycoses do not lose their pathogenicity as a rule, even after several years of subculturing, but old strains of dermatophytes gradually lose their pathogenicity Animal inoculations are done either percutaneously subcutaneously intravenously intraperitoneally intratesticularly and rarely subdurally It is desirable to follow the natural route of infection if possible, although it is not always practical. Experimental infection with the dermatophytes is best produced by the percutaneous route The subgingival route is desirable in experimental actinomycosis but it is not practical. It may not be necessary nor desirable to insufflate animals in order to produce an infection with *Coccidioides immitis* although ROSENTHAL and ROUTIEN stated that after instilling spherule-containing exudate with air pressure into the bronchi of guinea pigs, coccidiomycosis developed in the lung of every animal.

In the following pages, an outline will be given of commonly used techniques in the production of experimental infection in laboratory animals.

## DERMATOPHYTOSIS

Most studies in experimental mycology have been with dermatophytes. These investigations have greatly advanced our understanding of fungous

allergy and immunity The fundamental and classical studies are those of BLOCH J JADASSOHN SAEVES KOGOJ and JESSNER and HOFFMANN Several other investigators (SULZBERGER, W JADASSOHN) demonstrated, furthermore the dermatophylic tendency of the dermatophytes, not only after percutaneous inoculations but even after intracardial or intravenous injections. Using a special technique subcutaneous infection was produced by JESSNER and HOFFMANN Other clinicians have observed the involvement of the mucous membranes of the mouth by *Achorion* and involvement of bone, conjunctival and lymph node involvement and granuloma formation by *Trichophyton* (SEGUERRA TSCHERNAGUBOV COVISA KUNDRAT NOBL, PANAGIOTIS and PHOTINOS etc.)

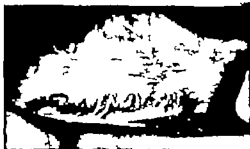
STERNBERG *et al* have shown recently that *T purpureum* (*rubrum*) can produce chronic granulatomous lesions in the omentum liver spleen, and muscles of mice after intraperitoneal injection This experiment confirms the findings of previous observers and challenges the concept of the obligatory dermatophylic tendency of the fungus Since fungi were found in the tissue 81 days after inoculation the classification of *T purpureum* as an obligatory superficial parasite remains questionable. It appears probable on the basis of several clinical observations that similar lesions may be produced in animals with other species of dermatophytes.

The following genera and species have been studied, among which *T gypseum* (*mentagrophytes*) and *T* (*Achorion*) *quinckeanum* are the most important from the immunobiological point of view

*T gypseum* (*mentagrophytes*)

*Susceptible animal* All small laboratory animals but the guinea pig has served best as a model

*Mode of infection* On shaved area, approximating 3 4 cm, of the guinea pig's skin a heavy emulsion of a 3–4 week old, highly sporulating fungus is rubbed



703. T gypseum infection in rabbit, two weeks after inoculation. The lesions are similar to that of the guinea pig The course of the infection is not as regular as in guinea pigs.

in with sandpaper without causing bleeding. Bloodless scarification with a scalpel may be used rather than sandpaper

*Course of infection* After 2–3 days, an acute dermatitis, at times associated with sero-sanguinous oozing is noticed, and is due mainly to trauma. On the 5th–6th day there is a noticeable infiltration and crust formation, persisting 2–3 weeks at times (Fig. 703), with an abundance of fungi in the scales and around the hair followed by gradual alopecia. Three weeks after the infection, a gradual clinical recovery is observed, which is associated with the complete disappearance of fungi.

The second inoculation has a shorter incubation time, a more severe reaction is produced, and the disease runs a shorter course. After the third infection the animal is generally immune although occasionally guinea pigs have to be reinfected 7–8 times before immunity develops (CATANEI and personal experience) The age, species, and the nutrition of the animal, the strain of the fungus and the quantity of inoculum all influence the course of the infection.



704 T purpureum infection in a castrated rabbit, five months after inoculation.

*T purpureum*

*Susceptible animals and course of infection* All small laboratory animals are susceptible but the infection is short-lived. When rabbits were castrated (REISS) an infection was established which lasted up to 14 months (Fig 704) However in recent experiments in which a different strain was used these results could not be duplicated. The strain of the organism and the nutritional state of the animal may not be the sole factors which result in a chronic infection in castrated rabbits. WHARTON *et al* produced chronic infection in rabbits by repeated inoculation of a heavy spore suspension on a large area of the flanks but this experiment has not yet been duplicated.

*T (endodermophyton) concentricum*

*Susceptible animals* monkey and guinea pig

*Mode of infection* similar to *T gypseum*

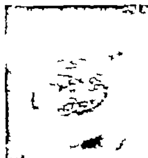
*Course of infection.* In guinea pigs, after the 10th day small erythematous patch appears and progressively increases in size. On the 17th day after inoculation, 5–7 mm. erythemato-squamous plaques are formed with clear-cut elevated edges. In the beginning the lesions consist of almost regular concentric circles but, in the third

week after inoculation, irregular sized but clearly outlined plaques are formed. In guinea pigs the infection disappears spontaneously after six weeks but in monkeys the infection may last up to 2½ months.

*Comment.* The production of experimental tinea imbricata with *T. concentricum* eliminated the genus *endodermophyton*. Furthermore, based on experimental evidence of OTA and KAWATSURE and FIGUEROA and CONANT, it was proposed that the plurality of the endodermophyton species should be reduced to a single species *T. concentricum*. However, it should be mentioned that OTA and KAWATSURE produced an endo-ectothrix microides infection in guinea pigs with *Endodermophyton concentricum*, an endothrix microides infection with *E. tropicale* and an ectothrix microides infection with *E. roquetti*. *E. indicum*, however, did not produce lesions in guinea pigs.

*Trichophyton (Achorion) quinckeanum*

*Susceptible animals.* Guinea pig, rabbit, mouse, rat, hen.



705. *T. gypseum* lesion produced in rabbit, twenty days after inoculation.
*(Lucille K. Georg—Atlanta)*

*Mode of infection.* Similar to *T. mentagrophytes*.

*Course of infection.* In guinea pigs, 4–5 days after inoculation an intense erythema is noticed, often but not always followed by the formation of small scutula. Around the 10–12th day a large plaque is formed which reveals a superficial erosion after removal. Some animals look sickly and also lose weight. This is followed by a spontaneous gradual disappearance of the inflammatory process, followed by a marked desquamation and partial alopecia. After 3 weeks a mild erythema is still noticeable. In 4–6 weeks the guinea pig is fully recovered and hair starts to grow again. In rabbits the course of the disease is prolonged. It is noteworthy that SULZBERGER found fungus elements in the blood of infected guinea pigs from the 1st to the 15th day with peaks on the first and about the tenth day after percutaneous inoculation. Guinea pigs respond to reinfection with *T. quinckeanum* in a manner almost similar to the response to *T. mentagrophytes*. The infection runs a rather irregular course in rabbits; the incubation time varies between 5–10 days, and the inflammatory response is less violent than in guinea pigs. Despite masses of scutula, spontaneous recovery is delayed. All this has no appreciable bearing on immunological phenomena.

The following *Achorions* produced only temporary but typical scutula in guinea pigs rats and mice *A. schoenleini A. violaceum*. *A. caninum* produces confluent scutula in dogs and mice, sometimes associated with deep necrosis which occasionally results in the death of the animals. The mouse is also susceptible to the organism. *A. formosum* can be transmitted to rabbits with typical scutula formation of short duration.

*Favotrichophyton album* (Tr discoides var album)
*Susceptible animals* Guinea pig and rabbit.

*Mode of infection* Similar to *T. gypseum*
*Course of infection.* According to G[illegible] and WORK lesions in guinea pigs actually increase in size during the second week, at which time a piling up of thick white and silvery scales is noticeable. In some instances small crusts are formed. The removal of these crusts is painful and exposes tiny erosions covered by a serous and seropurulent exudate. Scaliness and crust formation persist up to 36 days and there is no healing tendency FOWLE and SHORAK produced similar lesions in rabbits (Fig. 705).

*Microsporum lanosum*
*Susceptible animals* Kittens puppies and other young laboratory animals.

*Mode of infection.* Similar to *T. gypseum* (*mentagrophytes*)
*Course of infection* 3–5 days after inoculation a severe inflammatory reaction is produced, with heavy crust formation on about the 17th day There is also gradual involvement of the hair resulting in partial alopecia. All animals recover from the infection in about 30–50 days in contrast to the longer and often less inflammatory course of the natural clinical disease in kittens, and puppies.

The following microsporons have been used for experimental purposes with results similar to those described above *M. fulvum M. villosum M. pubescens M. [illegible]* and *M. niveum* BLOCH succeeded in producing a temporary infection in new born rats with *M. audouini* KLEINERT produced an abortive infection in guinea pigs with *M. pertenue* (probably a variety of *M. audouini*) infected hair

## CANDIDASIS (MONILIASIS)

Experimental investigations with yeasts and yeast like organisms are rather confusing and difficult to analyse This statement applies particularly to the *Candida* group. With the exception of *C. albicans* which has been studied extensively most species of the *Candida* genus are not considered frequent pathogens and require a more thorough experimental study The following species are pathogenic to some laboratory animals.

*Candida albicans*
*Susceptible animals* Rabbit mouse.

*Mode and course of infection.* Intracutaneous injection of heavy spore suspension (1 ml) is followed by abscess formation in 48 hours in both rabbits and mice. Intravenous injection kills the rabbit in 4–5 days with miliary abscess formation in the lungs, kidneys and other parenchymatous organs.

*Candida pinoyi*

*Susceptible animal* Rabbit.

*Mode and course of infection.* An intraperitoneal injection of 1.0 ml of a heavy spore suspension (500,000 organisms per ml) produces an acute peritonitis and death of the animal (URSO and CAPOCACCIA).

*Candida metalondinensis*

*Susceptible animal* Rabbit.

*Mode and course of infection.* An intrapulmonary injection of 0 5–1.0 ml of a thick suspension is made through the thorax of the animal by means of a syringe. The fungus does not produce a lethal infection but, sacrificing the animal 15–20 days after infection, a definite lung involvement is noticed This consists of several whitish nodules. Some are caseous and some of the nodules coalesce. A noticeable congestion of the lung is present between the nodules. The process extends to both lungs but the inoculated side shows larger nodules (CASTELLANI).

## CRYPTOCOCCOSIS (TORULOSIS)

*Cryptococcus hominis*

*Susceptible animals* Mouse, rat.

*Mode of infection* Either material from patients (centrifuged spinal fluid) or a heavy saline suspension of cultures should be injected intraperitoneally or intravenously

*Course of infection* in mice after intraperitoneal injection The disease develops rather slowly BENHAM observed only involvement of the spleen, working with less virulent strains. Besides small grey abscesses this organ is also covered with gelatinous coating The more virulent strains also invade the lung, forming abscesses which eventually reach the central nervous system Fungi can also be recovered from enlarged peritoneal nodes and from gelatinous masses in the mesentery Death occurs in 3–4 weeks

## BLASTOMYCOSIS

*Blastomyces dermatitidis*

*Susceptible animals* Mouse guinea pig and rat

*Mode and course of infection* Intravenous, intratesticular and intraperitoneal injections are administered with a heavy suspension of the yeast phase grown at 37° C. For intravenous injection it is recommended that the dosage should not exceed 0.5 ml because sudden death may occur due to embolism of the fungi After intraperitoneal injection in mice the animals may die between 10–21 days but this is not a rule (SPRINZ and personal observation) Some survive the infection or die only after several months. However the disease *always* develops and reaches its peak around the 3rd week. Morbid anatomical changes consist of several small caseous nodules near the root of the mesentery or isolated points in the peritoneal cavity At times the disease may become generalized, spreading to the testicles, liver spleen, kidneys and lungs, and occasionally nodules may develop at the site of inoculation.

## SOUTH AMERICAN BLASTOMYCOSIS

*Blastomyces brasiliensis (Paracoccidioides brasiliensis)*
*Susceptible animals* Mouse guinea pig

*Mode and course of infection* CONANT prefers white mice and recommends intraperitoneal injection with 1 ml of a 1 2000 suspension (by volume) of the yeast phase of the fungus. Spontaneous death occurs only rarely around the 50th day The morbid pathology is characterized by the formation of yellowish nodules in the liver spleen, on the diaphragm and mesentery Lung infection has not yet been recorded in mice. On the whole the disease runs a mild course and has a tendency to spontaneous resolution. MONTEMAYOR was able to produce a specific orchitis in guinea pigs and LACAZ succeeded in causing a systemic infection in mice after intravenous inoculation of a concentrated suspension of cultures of *P brasiliensis cerebriforme* The lesions are of the septicemic type and present a certain uniformity of lesions localized especially in the spleen, liver lungs and lymph nodes.

## SPOROTRICHOSIS

*Sporotrichum schenckii*
*Susceptible animals* White and grey rat, mouse, cat, dog monkey

*Mode and course of infection.* The most suitable animal is the white male rat. Intratesticular or intraperitoneal inoculation of 0.5–1.0 ml of a heavy spore suspension of the mycelial phase is recommended. In 14–20 days the inoculation is usually



706. Sporotrichosis in the rat.
Note several granulomas in the mesentery and bilateral orchitis.

followed by abscess formation in the pelvic region and, later of the mesenteric lymph nodes spleen and the liver (Fig 706). Frequently ulcerative lesions develop along the tail at this stage. The animals rarely survive the 4th week. NORDEN found the intraperitoneal injection of the yeast phase grown on a brain-heart infusion agar at 37 C more suitable A stock suspension of the organisms was obtained by suspending the growth from one brain-heart infusion agar slant in 1 ml of buffered saline. This suspension killed nine out of ten mice within 18 days. Mice receiving 0 1 or 0.01 ml of this stock suspension survived up to 6 months but finally died. A heavy suspension of the mycelial phase injected intraperitoneally into mice results in death within 18–25 days.

## COCCIDIOIDOMYCOSIS

*Coccidioides immitis*

*Susceptible animals* Dog rabbit monkey rat guinea pig Also cattle sheep swine.

*Mode and course of infection* Several routes of infection have been proposed peroral administration (TAKAHASHI), subcutaneous injection (TAKAHASHI), percutaneous or intranasal inoculation (AHLFELDT) intranasal instillation and intraperitoneal inoculation (TAGER and LIEBOW) intratracheal insufflation (CRONKITE and LACK) and intratesticular inoculation (CONANT). The most suitable animal is the male guinea pig and the simplest procedure is the intraperitoneal injection. Most animals lose weight gradually and become rather inactive after the 10th day Death occurs between 3–4 weeks. The most conspicuous feature is orchitis, at times suppurating. In addition to that, an enlargement of the abdominal and mesenteric lymph nodes is noticeable with granuloma or abscess formation in the liver and pancreas The disease generally spreads to the lungs and appears macroscopically in the form of small greyish nodules.

## ACTINOMYCOSIS

Experimental data of actinomycosis are difficult to coordinate because of the confusing nomenclature and the multiplicity of species which have been used. As a result of recent investigations it seems justified that mainly two species should be considered as the causative agents of human actinomycosis *Actinomyces bovis* and *Nocardia asteroides* The following are the available data of experimental transmission of the disease in small laboratory animals

*Actinomyces bovis*

*Susceptible animals* Guinea pig rabbit.

*Mode of infection* Because of the difficulty of maintaining or subculturing the anaerobic species little reliable data are available NAESLUND injected well saturated bouillon cultures intraperitoneally subcutaneously and into the anterior chamber of the eye of rabbits

*Course of infection* In some instances only small, pea-sized tumours develop in the abdominal cavity of the guinea pig 60 days after intraperitoneal injection. In some

guinea pigs *and actinomycotic granulomas* the size of a chestnut develop occasionally. Histologically and mycologically they reveal the characteristic features of human actinomycosis. However the infection does not kill the animals. Inoculation into the anterior chamber of the eye caused turbidity of the aqueous humor in some rabbits and pronounced injection of the blood vessels of the cornea after two weeks in some rabbits. The disease remains localized and, 4–5 weeks after infection, autopsy shows thickening of the lens which is composed microscopically of granulation tissue with some interspersed actinomycotic filaments. It is of interest to note that infection cannot be produced in rabbits or guinea pigs after intravenous injection or after inhalation of large doses of pure cultures. (In cattle, however a progressive actinomycosis develops with this strain after subcutaneous injection.) Subcutaneous injections are of no avail in rabbits and guinea pigs.

*Nocardia asteroides*

*Susceptible animals* Guinea pig rabbit.

*Mode of infection* A well triturated, heavy suspension (3–7 ml) is either injected intraperitoneally into the guinea pig or intravenously (into the marginal vein of the ear) into rabbits. Intravenous injections should be repeated at weekly intervals for 3–5 weeks. Two intraperitoneal injections, given within one week, are generally sufficient to produce the disease in guinea pigs.

*Course of infection.* Some animals will develop external or visceral lesions with granules and some only temporary changes. It is still an open question as to which factors play an important role in establishing a fatal infection. N[illegible] claims that rapidly induced fatal infection could be produced in both guinea pigs and rabbits after intravenous injection with strains which were subjected to several animal passages. Inoculations continued over a longer period of time (NAKAYAMA) seem to be more effective than giving large doses for a short time. Apparently the establishment of lesions depends largely on the degree of sensitization of the animal. There is evidence that a high antibody content of experimental animals does not protect against infection (MILLER and DRAKE). It is also possible that secondary microbic invaders may enhance the development of infection ([illegible] EVENSEN). The clinico-pathological changes produced by *Nocardia* are identical with those of *A. bovis*.

## MYCETOMA

Several genera are the causative agents of this disease but only a single species *Monosporium apiospermum* has been used successfully in animal experimentation. Most fungi isolated from mycetomas (except *Nocardia asteroides*) are not considered pathogenic for laboratory animals.

*Monosporium apiospermum*

*Susceptible animal* Rabbit.

*Mode and course of infection* Intraperitoneal and subcutaneous injection of spore suspensions produces sclerotic, granulomatous nodules (TAROZZI). Similar changes were produced by VIDARI after intravenous injection of a spore suspension. C[illegible] injected a saline suspension of spores into both knee joints with the sub-

followed by abscess formation in the pelvic region and, later of the mesenteric lymph nodes spleen and the liver (Fig. 706). Frequently ulcerative lesions develop along the tail at this stage. The animals rarely survive the 4th week. NORDEN found the intraperitoneal injection of the yeast phase grown on a brain-heart infusion agar at 37 C more suitable. A stock suspension of the organisms was obtained by suspending the growth from one brain-heart infusion agar slant in 1 ml of buffered saline. This suspension killed nine out of ten mice within 18 days. Mice receiving 0 1 or 0 01 ml of this stock suspension survived up to 6 months but finally died. A heavy suspension of the mycelial phase injected intraperitoneally into mice results in death within 18–25 days.

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*Mode of infection* Because of the difficulty of maintaining or subculturing the anaerobic species, little reliable data are available. NAESLUND injected well triturated bouillon cultures intraperitoneally subcutaneously and into the anterior chamber of the ey[illegible] of [illegible]bbit

*Course of infection* I[illegible] instances, only small, pea-sized tumours develop in the abdominal ca[illegible] the guinea pig 60 days after intraperitoneal injection. In some

*Course of infection* Intraperitoneally inoculated mice develop large granulomas in the abdominal cavity the location corresponding to the site of injection. Smaller granulomatous structures may be found within the adherent omentum. These animals do not show signs of a systemic spread of the infection except for vascular congestion of lungs, kidneys, liver and spleen. Intravenously infected mice develop granulomatous lesions of the lungs and kidneys. MILTON THIAGO DE MELLO produced a generalized infection and death in white mice after intraperitoneal injection (0 4 ml of heavy suspension) (Fig. 707 708). Granulomatous nodules containing abundant fungi were found in the mesentery testicles and some ribs. The subcutaneous route was chosen by O'DALY who injected one drop of a spore



707 Fonsecaea pedrosoi infection in mice, 28 days after infection. Note the dissemination of lesions in the abdominal cavity and necrosis of the abdominal wall.
(*M Th de Mello–Rio de Janeiro*)

emulsion intradermally into the base of the tail of rats between the caudal veins. After 48 hours a temporary oedema and erythema developed. After 3–4 weeks the circumference of the tail became rough, thickened and scaly Although verrucous lesions are not produced and the disease disappears spontaneously the microscopic changes resemble those of human chromoblastomycosis.

## HISTOPLASMOSIS

### *Histoplasma capsulatum*

*Susceptible animals* Guinea pig white mouse, rat, dog (particularly puppies) and monkey HOWELL obtained more uniform results with inbred male mice (DBA line 1) which were suitable for the measurement of the virulence of a given strain. The percentage of mortalities is high.

*Mode and course of infection* A suspension of the yeast phase of a 5–6 day-old culture is recommended. Mice are preferable The disease almost always develops after the intraperitoneal inoculation, and the outcome depends largely on the virulence of the strain and the amount injected HOWELL recommends intracerebral injections and prefers males of the dilute brown strain (DBA line 1) For the inoc

ulum, viable organisms are estimated from plate counts. Fifty percent of mice injected with 20 000 or more organisms die between the 7–10th day 50 % of these mice injected with less than this number of organisms survive for at least 19 days. The first sign of the disease is a gradual loss of weight. There are no skin manifestations or any gross lesions at autopsy A granular meningitis of varying intensity is an almost constant finding The meningitis may extend to the spinal cord region. In the liver a patchy necrosis develops in the parenchymal cells. The spleen and liver show a marked reticulo-endothelial hyperplasia with a large number of phagocytized organisms. DE MONBREUN produced the disease in monkeys after intravenous injection of a broth suspension of a 3 day culture from blood agar A rapid emaciation followed with marked enlargement of the lymph nodes, and death occurred on the fourteenth day after inoculation. Parasites were found not only in the enlarged liver spleen and lymph nodes, but the bone marrow also showed an enormous number of intracellular parasites. DE MONBREUN also succeeded in transmitting the disease to dogs and puppies by feeding them cultures of both forms of the fungus.

*Remark.* Although dogs are considered to be carriers of *Histoplasma capsulatum* experimental transmission to adult animals is not always successful.

## METHODS FOR ENHANCING EXPERIMENTAL INFECTION

Although a large number of fungi are pathogenic for both man and laboratory animals there is still a search for an infective technique that will insure a consistently uniform and high rate of infection and/or mortality It is particularly desirable in relation to dermatophytosis since all past efforts to produce a chronic dermatophytosis in animals have been rather unsatisfactory

### *Effect of vitamins*

Although numerous in vitro studies have been conducted of the effect of vitamins on the growth of pathogenic fungi, animal experiments dealing with these factors are rather scarce. OTAKA fed rats on a vitamin B-deficient diet. After inoculation with *Sporotrichon schenki* a more severe visceral involvement was observed as compared with the controls. There was no clinical difference in animals infected with *T gypseum* and *T radiolatum* but the course was prolonged in the vitamin-deficient animals. According to JOYEUX and SAUTET *Microsporum felineum* infected guinea pigs kept on a vitamin-A-deficient diet showed a more severe reaction than the control animals BENHAM inoculated vitamin-deficient rats intraperitoneally with a strain of *Cryptococcus* isolated from a normal human skin. This organism produced a perisplenitis with a gelatinous exudate loaded with parasites which was similar to that caused by some pathogenic strains in normal rats.

### *Effect of Cortisone ACTH and X Ray*

Several reports (KLIGMAN W JADASSOHN MIESCHER REISS) deal with the effect of cortisone but this drug has not appreciably altered the course or severity of experimental dermatophytosis in guinea pigs However

REDAELLI found a more severe infection in cortisone treated rats inoculated with *C immitis* as compared with the controls. In the control animals a subcutaneous injection of an emulsion of *C immitis* produced a local fibroblastic granuloma without general infection. When rats were treated with 5 mg of cortisone daily for three days prior to the inoculation, and for 17 days after the inoculation, the infection was more severe. The subcutaneous granuloma showed large necrotic foci without the formation of fibroblastic tissue. Such animals had extensive visceral improvement. The combination of cortisone and X ray irradiation was successfully used by STVERATON who produced a rapidly progressive lethal infection with *Blastomyces dermatitidis* and *Candida albicans* A single massive dose (400 R) of X ray and 4 milligrams of cortisone are administered simultaneously to Swiss Albino mice (C.T W strain) Mice infected with *C albicans* succumb within 9 days and those infected with *Blastomyces dermatitidis* also develop a lethal infection with an average survival time of 7 4 days. Similarly BRANDT



708. H. pedrosoi infection in hamster 72 days after inoculation. Note the caseous nodule on the epididymis.

*(M Th de Mello–Rio de Janeiro)*

used X ray irradiation to produce systemic histoplasmosis with a South American strain which otherwise caused only a local reaction that healed in a relatively short time. In four species of animals white mice, gerbils (*Tatera brantsii*), stripped mice (*Rhabdomys pumilis*) and guinea pigs systemic histoplasmosis consistently developed after intraperitoneal inoculation and X ray treatment.

*Effect of gastric mucin*

The suggestion of MILZER and LEVINE to use mucin as an enhancing agent for bacteria was successfully applied by CAMPBELL and SASLOW and HOWELL and KIPKIE for fungi. For intraperitoneal injection, 0.5 ml of a suspension of the fungus in 5 % mucin is recommended. This dose corresponds to approximately 3,500,000 organisms and about 66.6 mortality occurs using white Swiss mice (Bagg strain). MEYER and her co-workers consistently produced intraperitoneal nodules in mice after intraperitoneal injections of actinomyces bovis suspended in mucin. This method was also used by STRAUSS and KLIGMAN Infection of *Nocardia asteroides* in a gastric

mucin suspension in a concentration of 1 : 50 by volume was invariably fatal. Similarly, the yeast phase of *Blastomyces dermatitidis* in a concentration of 1 : 100 caused death within 10 days. *Coccidioides immitis* also produced 100% mortality when injected in a 1 : 100 concentration of gastric mucin. A gastric mucin suspension of *Sporotrichum schenkii* caused death in 50% of the animals within 10 days. *Cryptococcus neoformans*, suspended in a 1 : 100 concentration of gastric mucin, not only produced far more extensive lesions, but also shortened the survival time and always caused death. *Candida albicans* suspended in gastric mucin caused death in mice in 48 hours. A similar enhancing effect was produced with *Paracoccidioides brasiliensis*, *Hormodendrum pedrosoi*, *H. compactum* and *Phialophora verrucosa*. *Haplosporangium parvum*, which has an antigenic relationship with *C. immitis*, was injected in a 1 : 100 concentration. No mortality was observed in the mice, but numerous nodules were found.

These favourable results with gastric mucin are quite encouraging and may be applied advantageously for chemotherapeutic assays. The method may serve also as a diagnostic tool with ground human tissue which at times harbours only few fungous elements. In such instances, cultures are uncertain and injections of a saline suspension are equally unreliable.

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# TRICHOPHYTOSIS OF THE SMOOTH SKIN

## (Tinea glabrosa)

LIBERO AJELLO

Atlanta (Georgia)

The species of the genus *Trichophyton* Malmsten, 1845 are characterized by their ability to invade the keratinaceous tissues of animals. Although this chapter is concerned solely with Trichophyton infections of the smooth skin, it should be borne in mind that the various members of this genus may also invade nails and hair and in fact, only rarely parasitize smooth skin.

All available evidence indicates that Trichophyton infections are transmitted from person to person or are contracted from infected lower animals such as cows, horses and rodents. However MUENDE and WEBB's isolation of *T. mentagrophytes* from debris in a cow barn, leads one to speculate that perhaps some of the *Trichophytons* exist primarily as saprophytes in soil. If this is true soil may have to be considered as the reservoir of infection for susceptible animals.

### SUBDIVISION AND EPIDEMIOLOGY

Approximately eight species of *Trichophyton* are known to cause tinea glabrosa. *These species are*

*T. mentagrophytes* (ROBIN) BLANCHARD 1896
*T. rubrum* (CASTELLANI) SABOURAUD 1911
*T. schoenleinii* (LEBERT) LANGERON and MILOCHEVITCH 1930 [1]
*T. tonsurans* MALMSTEN 1845
*T. verrucosum* BODIN 1902 [2]

[1] Valid name for Achorion schoenleinii
[2] Name validated by AINSWORTH and GEORGE for T. [illegible]iforme SABOURAUD 1893

*T violaceum* SABOURAUD 1902,
*T ferrugineum* (OTA) LANGERON and MILOCHEVITCH 1930
*T concentricum* BLANCHARD, 1896

Several of these species *T mentagrophytes* *T rubrum* *T verrucosum* and *T tonsurans* are world-wide in their distribution, being found on all continents. One species *T ferrugineum* is only known from Asia and Africa, while *T concentricum* occurs in Asia, certain Pacific Islands, and S America. The other Trichophytons, *T schoenleini* *T viola-*



709 Ringworm lesion marked by erythema and scaling.

*ceum* are found commonly in Europe, Africa, Asia, S America and only rarely in the United States.

Several other species of Trichophyton have been described *T gallinae* (MEGNIN) GEORG, 1952, *T megnini* BLANCHARD 1896, *T gourvili* CATANEI, 1933 *T soudanense* JOYEUX, 1912, etc., but they are either too little known, or too infrequently invade the smooth skin to be included in this discussion.

## SYMPTOMATOLOGY

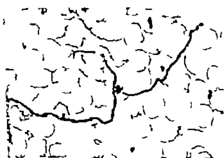
*Tinea glabrosa* presents various symptoms, depending upon the aetiological agent and the reactions of the host to the parasite, the severity of which may be affected by prevailing climatic conditions. The lesions

persist for many years for apparently these individuals fail to develop resistance to the parasite. *T concentricum* classically produces a skin



711 Extensive T rubrum infection of the back.
(*Samuel–Dmeda*)

disease characterized by the development of papulo-squamous patches which develop scaling in a pattern of concentric, imbricate rings. Favus, caused by *T schoenleini* is usually localized on the scalp



712. Mycelial elements in skin scrapings treated with NaOH

where it shows so-called *scutula* i.e. yellow perifollicular cup-shaped crusts leaving atrophy However they may also occur on the glabrous skin (Figs. 714 and 715).

Deep suppurative lesions characterized by the development of reddish nodules and perifollicular pustules (*agminate folliculitis*) are frequently observed in *T. mentagrophytes* and *T. verrucosum* infections contracted from cattle.

Various types of *allergic phenomena* may accompany *Trichophyton* infections and must be taken into account in making a diagnosis.

## DIRECT EXAMINATION

The mycotic nature of suspected lesions is established by microscopic examination of skin scrapings. The affected area should be prepared by swabbing with a sponge soaked in 70 per cent alcohol. This washing serves to remove dirt and any medication that would make mi



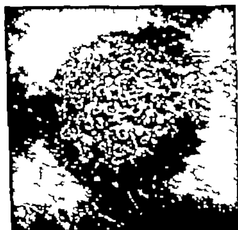
713. Hotchkiss–McManus stained preparation showing extent of mycelium in skin.

croscopic examination difficult. After drying, the lesion is scraped with a sterile scalpel. The scales so obtained are placed in a suitable sterile container and are held available for microscopic and cultural study.

For microscopic examination several scales are placed in a drop of 10 per cent sodium or potassium hydroxide on a slide and covered with a coverslip. The preparation is then gently heated over a low flame just short of boiling to hasten the clearing action of the alkali. The slide is examined under the lower powers of the microscope for the presence of mycelial filaments and arthrospores. The mycelial elements of the *Trichophytons* in skin are septate, variable in length, with a uni

form diameter of 4–6 μ and on occasion differentiated into arthrospores (Figs. 712 and 713)

*The finding of mycelial filaments in skin scrapings indicates the mycotic nature of the infection but does not reveal the identity of the aetiological agent since all members of the genus Trichophyton produce identical structures in the skin* The species involved can only be determined by culture.





714–715 Tinea favosa of the glabrous skin caused by T schoenleinii. Note honeycomb appearance and cup shaped scutula.

(*Siemens–Leyden*)

## CULTURE

With few exceptions, most species of the genus *Trichophyton* are readily cultured on a wide variety of media. A simple peptone-dextrose agar designated commercially as Sabouraud agar is the standard isolation medium[1]

It is obtainable in dehydrated form from several commercial companies. The addition of 40 units of penicillin and 20 units of streptomycin per ml of medium is recommended to prevent the growth of contaminating bacteria that might otherwise prevent the development of the aetiological agent. For the isolation of *T verrucosum* and *T violaceum* both deficient in their abilities to synthesize thiamine, the use of a thiamine-enriched dextrose agar is recommended

Sabouraud Dextrose Agar Formula Dextrose 40 g, Peptone 10 g, Agar 15.0 g, Distilled Water 1,000 0 ml.

Thiamine – Dextrose Agar Formula Dextrose 40.0 g Peptone 10 0 g, Thiamine 0.001 g, Agar 15.0 g, Distilled Water 1,000.0 ml

Procedure for both media. – Dissolve ingredients in a water bath place 8 ml in an 18 × 150 mm test tube. Sterilize by autoclaving 10 minutes at 120°C, and slant. A temperature of 25°C is recommended for incubating the cultures but *T verrucosum* develops best at 37°C.



716. Colonies of *T mentagrophytes* growing on dextrose peptone agar Typical granular colony on left and cottony type on right.

The various species of Trichophyton are identified on the basis of their macroscopic and microscopic characteristics.

**DESCRIPTION OF SPECIES:**

*T mentagrophytes* (ROBIN) BLANCHARD 1896

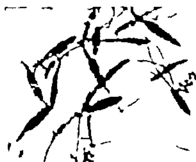
Rapidly growing, producing a flat, disc like colony with surface colour



717 Microconidial clusters produced by *T mentagrophytes*.

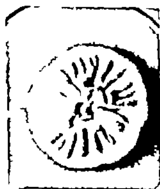
ranging from white to cream, tan, yellow and occasionally orange, pink or red Texture of surface powdery granular or cottony (Fig 716).

Reverse pigmentation usually rose-brown, but some strains yellowish, orange or red. Microscopically microconidia numerous, small, globose, 2-5 μ diameter are singly or in clusters (Fig 717) Multiseptate, club-



718. Multicelled macroconidia of T mentagrophytes.

shaped macroconidia rare or abundant, depending upon the strain, 6 to 12 μ in width and 20 to 60 μ in length (Fig 718) Macroconidial formation may be induced by growth on wort agar [1] Non-specific structures such as chlamydospores, nodular bodies, spirals and racquet mycelium may also be produced.



719 Granular type colony of T rubrum.

*T rubrum* (CASTELLANI) SABOURAUD 1911

Slow growing, producing a flat, or heaped colony with a white, fluffy surface (Fig 719). Some strains have a folded surface which is

[1] Obtainable commercially from several sources in dehydrated form.

powdery to granular and develop considerable red pigment. Reverse of the colony is typically reddish purple, rarely colourless Microconi-



720 Gro p of narrow pencil shaped macroconidia of T rubrum

dia rare to abundant, clavate 2–4 μ borne acropleurogenously Macroconidia rarely produced but may be abundant in reddish powdery strains usually elongated, thin-walled with blunt ends, 4–6 μ wide, 10–



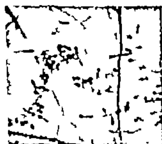
721 Three colonial types of T t ms rans derived from a single spore culture Surface configurations range from cratent orm to acuminate to cerebriform

90 μ long (Fig 720) Production frequently induced by growing 4–6 weeks on heart infusion tryptose agar [1]

Beef heart, Infusion from 500 0 g, Trypt se 10.0 g, Sodium chloride 5 0 g, Agar 15.0 g Distilled water 1 000 0 ml (A ailable in dehydrated form from commercial sources).

*T tonsurans* MALMSTEN, 1845

Fairly rapid growth, producing variable types of colonies usually heavily folded with an acuminate or crateriform centre (Fig 721) Surface usually powdery of variable pigmentation, ranging from tan to



722. Microconidia of T tonsurans.

white, yellow or rose. Reverse reddish brown, yellow or purplish. Microconidia numerous, usually clavate, but highly irregular in size and shape, 3–8 μ in length by 1.5–4 μ in width Macroconidia rare



723 Rare macroconidium of T tonsurans [illegible]

thin walled, smooth Induced on wort agar 4 8 μ by 20 50 μ (Fig 723) Chlamydospores numerous

*T schoenleini* (LEBERT) LANGERON and MILOCHEVITCH 1930

Slow growing Colony heaped and folded Early growth frequently

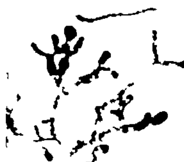
submerged. Surface moist and glabrous at first, becoming powdery or slightly downy white, cream or tan in coulowr (Fig 724) Microconidia and macroconidia absent. On whole grains and rice, microconidia oc



724 Heaped and folded colony of T schoenleini

casionally formed, appear small and globose 2–4 μ diameter Chlamydospores numerous, tips of hyphae frequently clubbed and branched and designated as favic chandeliers" (Fig 725) Numerous chlamydospores

*T violaceum* SABOURAUD 1902.



725 Characteristic "favic chandeliers produced by T schoenleini.

Slow growing heaped, heavily folded, waxy-smooth and cream coloured at first, gradually becoming a deep violet (Fig 726) With age, pigment is lost and colony becomes powdery or cottony

Microconidia few on usual media but numerous on thiamine enriched media and whole grains, small, clavate, 1–2 by 2–3 μ borne laterally and in clusters. Macroconidia absent on ordinary media, production in low numbers induced by growth on thiamine enriched media or whole grains, irregular to clavate in form 2–4 μ wide and 5–30 μ long, few to many-celled (Fig 729) Chlamydospores numerous. A form properly designated as *T violaceum* variety *glabrum* is described



726. Heavily folded, waxy colony of T violaceum with non-pigmented pleomorphic sector

from N Africa. Primary growth is greyish with a moist surface with few or no microconidia. Numerous chlamydospores.

*T verrucosum* BODIN, 1902.

Colony develops very slowly in three general types. Heaped and folded (variety *album*) verrucose (variety *ochraceum*) or flat (variety *discoides*). Surface white, tan or yellowish, first moist and glabrous, later becoming powdery or slightly downy (Fig 727–728) Microconidia rare on ordinary media, may be numerous on thiamine enriched media and whole grains, small, clavate, borne singly or in clusters. Macroconidia absent on usual media, few on enriched media, thin-walled, highly irregular in shape, 10–40 μ long 2–8 celled (Fig 730). Numerous chlamydospores.

*T ferrugineum (Ota)* LANGERON and MILOCHEVITCH, 1930

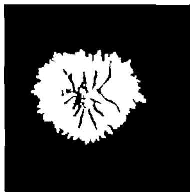
Slow growing, glabrous waxy and heavily folded (Fig 731) Pigmentation variable – reddish to yellow Microconidia rare, pyriform to subglobose, 2–3.5 μ. Macroconidia absent. Chlamydospores abundant.

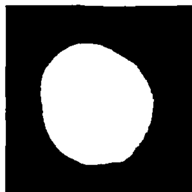
*T concentricum* BLANCHARD 1896

Slow growing, glabrous becoming downy deeply folded, surface whitish to yellowish in colour reverse light to deep amber (Fig 732) Microconidia and macroconidia unknown. Chlamydospores present.

## DIAGNOSIS

The diagnosis of tinea glabrosa rests on the correlation of clinical signs with the demonstration of the presence of the causative agent by microscopic and preferably by cultural means The discovery of the aetiological agent is important as many non mycotic conditions may closely simulate the clinical appearance of tinea glabrosa. This disease





727–728 T verrucosum (or T faviforme). Heaped and folded colony on left grown on plain dextrose-peptone agar Colony on right shows effect of growth on thiamine-dextrose-peptone medium

must be differentiated from pyodermas, pityriasis rosea, psoriasis, contact dermatitis, drug eruptions erythema annulare, seborrheic dermatitis, even secondary syphilis, all of which can be excluded by demonstrating mycelial elements in the skin either directly or by culture.

## THERAPY

Treatment should be conservative. Any co-existing bacterial infections should be eradicated before treating the underlying mycosis Medica-



729 Macroconidia of T. violaceum produced on thiamine enriched dextrose-peptone agar



730 Macroconidia of T. verrucosum (or T. faviforme) produced on a thiamine enriched medium.



731 Glabrous, folded colony of T. ferrugineum.



732. Deeply folded colony of T. concentricum.

tions are best applied after debridement of the lesions by scrubbing with soap and water. Preparations of unsaturated fatty acids containing propionic, caprylic or undecylenic acid, Whitfield's ointment, 5 per cent ammoniated mercury ointment or 3 per cent salicylic acid, are frequently successful in clearing up the condition in several weeks time. However it is important to continue treatment for a week or two after a cure seems apparent to prevent relapses. The medications should be rubbed in vigorously and applied several times daily for best results.

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# MICROSPORUM INFECTION OF THE SMOOTH SKIN

M. J. MARPLES
Otago, New Zealand

Tinea corporis, ringworm of the smooth skin, is an infection caused by several dermatophyte species including those of the genus *Microsporum*. This genus is the predominant cause of skin ringworm in most temperate areas, but is much less commonly found in sub-tropical and tropical regions. The lesions produced may be single or multiple and are often associated with a co-existent scalp infection. A large number of species have been described, many of which have been subsequently found to be variants, and CONANT and his co-workers have reduced the number to the following three species.

## I. MICROSPORUM CANIS BODIN

Synonyms.—*Microsporum felineum* NEWBORN, *Microsporum lanosum* SABOURAUD, *Sabouraudites lanatus* LE BASQUE.

This species is the most common cause of microsporosis of the glabrous skin. Lesion can occur at all ages, but children show a greater susceptibility than adults. Associated scalp lesions are often present.

### EPIDEMIOLOGY

The infection is not confined to man, but frequently occurs in cats and dogs, especially in the young of these species. Adult and even young domestic pets may show no obvious lesions, and the infection can only be detected by careful examination under Wood light. Patients frequently give a history of contact with an infected pet, and there is good evidence that the organism loses its virulence after relatively few human passages (LEWIS and HOPPER, STEVES and LYNCH). Several

members of a family may be infected but *M canis* does not give rise to widespread human epidemics In investigating a human case it is important to examine domestic pets so that the source of infection can be traced

## SYMPTOMATOLOGY

The lesions may be single or multiple They occur most commonly on the face and neck (MARPLES) and are sometimes associated with previous trauma. The classical lesion begins as a small papule which grows outwards to become annular with a healed centre and a definite raised



733 Classical annular lesion of Tinea corporis. Aetiological species Microsporum lanosum

*(Daphne Marshall-Dunek )*

red edge The ring may show fine or coarse scaling or may carry tiny vesicles. This type of lesion shows inflammatory reaction In other subjects the lesion may show no central healing and appear as a circumscribed patch of redness and scaling or if considerable inflammatory reaction is present may be boggy and crusted. There are usually few subjective symptoms but some patients complain of considerable itching and the lesion may become tender during vigorous treatment

## MYCOLOGY

### *Direct examination*

Scrapings should be taken from the advancing edge of the lesion. A blunt scalpel may be used or scales can be peeled outwards with forceps. The fragments of skin should be mounted in five to ten per cent. potassium hydroxide and warmed gently to promote clearing of the tissues. They are examined under low and high power of the microscope, using reduced illumination. The fungus appears as a branching septate mycelium, rarely segmenting into arthrospores. Lanugo hairs, if present in the scraping, have a mosaic of encrusting spores.



734 Slice culture of Microsporum × 135 Numerous thick walled spindle shaped macroconidia. Few microconidia. Enlarged × 2.

*(Daphne Marshall-Dowden)*

### *Culture*

Several tubes of Sabouraud glucose agar should each be implanted with three or four skin fragments taken from the edge of the lesion. Other suitable media are Sabouraud maltose agar or beerwort tellurite medium. To reduce contamination the lesions, or the scrapings after removal, may be washed with 70 per cent. alcohol before inoculation of the medium. This process, however makes the collection of material more difficult, and in this respect the use of multiple inoculations is found sufficient to ensure the development of the fungus in pure culture.

The tubes should be incubated at room temperature and examined every few days up to about three weeks. The colony of *M canis* grows

fairly rapidly It is visible in 2–3 days and can be examined microscopically in 5 to 7 days It remains circumscribed and shows a fluffy white aerial mycelium, which later may become buff and powdery Most strains produce a diffusible yellow or orange pigment which colours the surrounding medium. WALKER has however, described two other varieties, *M canis var album* which produces no pigment, and a citreus type which produces a reduced amount of pale yellow pigment. About 10 per cent. of the cultures grown in this department are of the non-pigmented variety WALKER also describes strains which give rise to dysgonic colonies which are small and brown and often without aerial mycelium. Two such dysgonic strains have been encountered in this area. WALKER states that these variants show an interesting geographical distribution and one of the rarer varieties may predominate in certain localities Pleomorphic changes develop fairly readily in cultures of *M canis*

If detailed morphological investigation is required it is more satisfactory to prepare slide cultures of the strain. The fungus is grown on a microscope slide or coverslip and can be examined *in situ* with minimum disturbance, so that the various structures remain in their natural positions. Methods of preparation of slide cultures have been described by LEWIS and HOPPER, LITTMAN, LA TOUCHE and several other workers

If tube-cultures are used, material for microscopic examination should be extracted with a needle or a hook. Care should be taken that the sample includes growth from the centre of the colony and adjacent to the medium, otherwise characteristic structures may not be included in the preparation. The specimen should be gently teased out on a slide and mounted under a coverslip in lactophenol cotton blue. Microscopic examination reveals a branching mycelium carrying abundant thick walled, fusiform septate macroconidia, the distal ends of which are roughened and carry irregular protuberances. These macroconidia are always present and may become so numerous that they give rise to the powdery appearance of older cultures. Clavate microconidia may be present, but are usually few in number Racquet hyphae, nodular organs and occasionally chlamydospores are found in older cultures

*Wood light*

Lanugo hairs, especially in a lesion which has been present for some time show the characteristic green fluorescence of microsporum spores.

## II. MICROSPORUM AUDOUINI GRUBY

Synonoms *Trichophyton decalvans* Malmsten, *Microsporum umbonatum* Sabouraud. This species very rarely causes the lesions of Tinea corporis and these if present, are almost always associated with those of



735 Alopecia due to M audouini
*(Carmen C Thomas – in Conant' Clin. Mycology)*

Tinea capitis. WALKER, however has recently recorded a series of cases of tinea corporis caused by *M audouini*

## EPIDEMIOLOGY

*Microsporum audouini* is an anthropophilic organism, mainly causing tinea capitis, the epidemiology of which will be discussed in a later chapter. Laboratory animals are relatively insusceptible and can only be infected occasionally and with difficulty. MURRELL has recorded spontaneous infection of a fox terrier with this species, but this appears to be a very rare phenomenon, and domestic pets play no part in the ecology of *M audouini*

## SYMPTOMATOLOGY

The lesions of the smooth skin are similar to those caused by *M canis* and cannot, clinically be distinguished from them. They are usually small, showing little inflammatory reaction and in most cases are found close to the hair line.

## CULTURE

Cultures should be prepared as described for *M canis* The colony grows slowly to form a compact velvety mycelium, with characteristic radial furrows The mycelium is white or cream at first, and later may become greyish or brown in colour The reverse of the colony may show brown or orange coloration. DUNCAN (1945) and WALKER (1950) have described dysgonic strains which develop very slowly and show little aerial growth. Pleomorphic changes are uncommon. Material for microscopic examination should be prepared as described for *M canis* In most strains macroconidia are scarce even in primary culture and are not found in subcultures HARE has described a strain isolated in England in which macroconidia were abundant. Typical macroconidia are elongated and contain few septa and do not show the distal roughening found in those of *M canis* Microconidia nodular organs and chlamydospores are frequently present

### *Wood light*

The appearance of *M audouini* under Wood light and in skin scrapings is indistinguishable from that of *M canis*

## III. MICROSPORUM GYPSEUM GUIDART and GRIGORAKIS

Synonoms *Achorion gypseum* Bodin *Microsporum fulvum* Sabouraud. *Microsporum gypseum* like *M canis* is a parasite not only of man, but also of domestic pets In most countries however the species is only rarely encountered but it is common in some areas of South America.

## EPIDEMIOLOGY

The fungus causes small family epidemics, but adults are relatively insusceptible and few adult infections are encountered. Puppies appear to be the most common source of infection. Experimental lesions can be produced fairly easily in guinea pigs but these heal spontaneously in a few weeks

SYMPTOMATOLOGY

The lesions caused by this species, while essentially similar to those due to *M. canis* tend to show less central healing, a vesicular margin and a greater inflammatory reaction, so that moist crusted areas are occasionally produced. Associated scalp infections may be present.

CULTURE

These should be prepared as described for *M. canis*. The culture grows rapidly and is extensive, eventually covering the entire surface of the medium. The surface is felted and brown in colour and often develops



736. Slide culture of *Microsporum gypseum* × 440
Macroconidia, thin walled, and very numerous.
(*Daphne Marshall-Dunedin*)

concentric furrows. Pleomorphic changes appear early. Microscopic examination reveals numerous thin-walled blunt-ended macroconidia, which are shorter and contain fewer septa than those of the other two species. Racquet hyphae, nodular organs and microconidia may be present.

MYCOLOGY

The appearance of *M. gypseum* under Wood light and in skin scrapings is indistinguishable from that of *M. canis*

## THERAPY

Microsporosis of the smooth skin readily responds to treatment. Almost any fungicide is effective, provided that it is vigorously applied. The lesion should first be gently washed with soap and water, etherial soap or 70 per cent. alcohol to remove scales and previous applications. The fungicide should then be rubbed well into the area. This should be repeated twice daily. Iodine, Whitfield's ointment, phenyl mercuric nitrate or acetate strength 1 in 1000 or 1 in 1500, ointments containing undecylenic compounds, dyes such as gentian violet all provide satisfactory topical applications. It should be noted that after a few days treatment the fungus can no longer be demonstrated by direct examination of scrapings, although cultures may remain positive. To prevent a relapse it is therefore important to continue treatment until the annular lesion disappears or merges into a general reddening of the area, and at least a week after a negative cultural examination is obtained. Fungicides can usually be applied even in the presence of an inflammatory reaction, but if this is severe, it is occasionally advisable to use a bland preparation such as zinc ointment or a dilute solution of potassium permanganate for a few days. This treatment should never be prolonged and should be followed by the vigorous application of some fungicidal preparation.

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# TINEA IMBRICATA

## (TOKELAU)

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### DEFINITION

*Tinea imbricata* or *Tokelau* is a fungus disease of the hairless skin, caused by *Trichophyton concentricum* and characterized by concentric circles of scales with geometrical regularity at least in the initial stages of the disease. Synonyms are *Tinea imbricata* (Asia, Oceania) *Tinea intersecta* (India, Ceylon) *Buckwar Oone Kunkune Gune Sala* (Gilbert Islands) *Gogo Gogo Gogowon* (Marshall Islands) *Cascado* (Molluccas, Java) *Gurap Kurab besi* (Malay States) *Lusung* (Borneo) *Pita* (Bourditch Island) *Lafa Tokelau* (Samoa) *Rodre Baeneradura Chimbert* (Brazil)

### EPIDEMIOLOGY

Tinea imbricata was originally considered a disease peculiar to Oceania, BONNAFY having even limited its geographical distribution to a very elongated triangle, the base corresponding to Sumatra and the apex reaching the islands of Tonga and Samoa. The original focus of the disease was, in fact, the Malay Archipelago from whence it spread, following the migratory currents of the Malay race, appearing successively in Indonesia and New Guinea, and many islands in the Pacific after one of which (Tokelau) the disease is also called, as well as to Burma, Ceylon, all the south of India, Indo-China, south of China and Formosa

According to MANSON (1892) the British navigator WILLIAM

DAMPIER in his book "Voyage Round the World" (1729) first de scribed the disease among inhabitants of the Philippine Islands and of the Marianas (Guam)

CHARLES WILKER of the United States Navy gave an interesting description of the disease which he observed in the Gilbert Islands in 1844

Until the middle of the nineteenth century the disease was still unknown in Tokelau it was brought there by a native from the Gilbert Islands. Because this native was named Peter the disease in this island is known as *Peta* From this island it spread, in 1869 to Samoa where it was observed by TURNER who called it *Herpes des quamans*

Outside the Asiatic continent, PIJPER found, in 1918 in South Africa, the first case of tokelau in a Kaffir

On the American continent the first cases of tokelau were observed in Brazil by PAES LEME (1903) and PARANHOS and LEME (1906) among the Indians of the Carajá tribe The Indians called it "*Roaro*" which means the "flying disease" because they believed it was blown to them by their enemies.

In 1917 ROQUETTE PINTO found the disease called *Bacucudáiá* among the Nhambiquaras Indians living in the state of Matto Grosso.

In 1924 DA FONSECA observed the disease under the name of *Chimberé* in another tribe of Indians, on the frontier between Brazil and Bolivia.

In 1938 MORA MORA reported a case in Columbia. In 1940 FIGUE RÔA and CONANT published another case from Guatemala.

In 1950 LEÃO and GOTO discovered tokelau among the Indians of the Uaurá tribe, living high up on the Xingú river in the state of Matto Grosso

The greatest focus of the disease in America is the central plateau of Brazil, consisting of a zone situated between the 10th and 13th parallels.

The occurrence of the disease in America must date from pre Columbian times with the migration from the Pacific islands and Asia through the Behring Straits (FONSECA, FIGUERÔA and CONANT) FIGUERÔA and CONANT regard the parasite as living saprophytically on the skin. In special conditions it may become pathogenic. This may

explain the occurrence of isolated cases such as those observed in Central America. The climate is one of the main factors in the epidemiology of tokelau. Heat, humidity and an average temperature of 28° C are optimal conditions for the invasion of *Trichophyton concentricum* in the human skin. The disease is not common in early childhood, infection usually taking place after the 6th year of age. In Brazilian Indian tribes, however cases have been observed in early childhood.

Tinea imbricata is contagious, spreading directly from man to man or indirectly through personal utensils of the patients. The indirect spread seems to be more common and explains the irregular distribution of the disease and the occurrence of isolated cases



737 *T. concentricum* direct examination of the scales.

**AETIOLOGY**

The presence of mycelial filaments in the scales of tokelau was first described by Fox (1874) who considered the parasite identical with European *Herpes circinatus* These facts were confirmed by KÖNIGER (1878). MANSON describing the disease in 1879 showed that it was different from European *Herpes circinatus* and that it was a separate clinical entity The mycelial formations of the parasite in the scales were seen afterwards by SABOURAUD (1894), who identified the disease with *Tinea trichophytica* Unfortunately none of these authors

managed to cultivate the parasite. TRIBONDEAU (1899) PINOY (1930) and WEHMER (1894) isolated *Aspergillus* from the scales of tokelau erroneously naming this contaminant *Aspergillus tokelau (Lepidophyton tokelau)* NIEUWENHUIS (1898) CASTELLANI (1910) HANAWA and NAGAI (1917) and others definitely demonstrated the trichophytic aetiology of tokelau, isolating the parasite from the scales. BLANCHARD (1896) named the fungus *Trichophyton concentricum* In 1910 CASTELLANI obtained cultures from four cases and reproduced the disease with one of the strains isolated

As the morphology of the fungus in culture is very simple, con-



738 *T. concentricum* Racquet hyphae and chlamydospores.

sisting almost exclusively of mycelial filaments and intercalated, and of terminal chlamydospores, not attacking hairs CASTELLANI classified it as the genus *Endodermophyton*

Later LANGERON and MILOCHEVITCH (1930) using natural media (barley grain) observed a sporing apparatus of the *Acladium* type

Thanks to OTA and KAWATSURE's experiments the parasite was classified under the genus *Trichophyton* Various species were described and distinguished only by their pigment production. This character however is secondary and disappears with successive subcultures and thus cannot be used to distinguish the species Mycologically they

are indistinguishable. There is only one *fungus* causing tokelau, *i.e.* *Trichophyton concentricum* BLANCHARD 1896



739 *T. concentricum* Hypha with enlarged extremity Spiralled hyphae are also seen

**SYNONYMS**

*Trichophyton concentricum* BLANCHARD 1896
Syn *Lepidophyton concentricum* GEDOELST 1902
*Aspergillus lepidophyton* PINOY 1903
*Trichophyton mansoni* CASTELLANI, 1905.
*Trichophyton Castellani* (PERRY 1907) CASTELLANI 1908
*Endodermophyton concentricum* CASTELLANI 1910
*Endodermophyton indicum* CASTELLANI 1911
*Oospora concentrica* HANAWA and NAGAI 1917
*Endodermophyton mansoni* CASTELLANI, 1919
*Arthrosporia tropicalis* GRIGORAKI, 1925
*Arthrosporia indica* GRIGORAKI 1925
*Endodermophyton Roquettei* FONSECA, 1925.
*Myxoderma concentricum* VUILLEMIN, 1929
*Myxoderma Roquettei* VUILLEMIN, 1921
*Ichorium concentricum* CIFERRI and GRIGORAKI, 1928.
*Ichorium indicum* CIFERRI and GRIGORAKI 1928

## MYCOLOGY

In the scales treated with a 10 % solution of potassium hydroxide the fungus appears as a multitude of septate mycelial filaments with a granular plasma.

When a culture is made in SABOURAUD's medium without any previous treatment, contaminants will easily overgrow the *Trichophyton concentricum*. *The fungus is isolated more easily by washing the scales with alcohol before the inoculation in Sabouraud's medium to which a* 0.1 % *crystal violet solution should be added.*

The growth of the fungus is slow, colonies appearing after 8–12 days. The colonies are cerebriform with small grooves which radiate to the periphery, cream or faintly pink in colour and covered with short, white hyphae. The base of the colony is like pale amber. There



740. *T. concentricum*: giant colony of 28 days.

is no diffusible pigment formation. The fungus grows well at 37 °C, showing moist cerebriform colonies with short, white hyphae. Microscopical examination shows a toruloid mycelium, which is more abundant than in the culture at 25 °C, and which is formed of septate and ramified hyphae of varying thickness with dilated ends, intercalated, and of terminal chlamydospores, nodular structures and loose spirals with an average of three or exceptionally six windings. Formations like *favic chandeliers* may occasionally be found.

## SYMPTOMATOLOGY

It is not always possible to observe the initial lesion of tokelau. MANSON, who transmitted the disease to man by the inocu-

lation of scales, observed the appearance of a slight erythema at the point of inoculation after about one week. The erythema turned into a greyish papule of about 6 mm in diameter very itchy and tending to vesiculation.

With the development of the lesion the centre fades, a circle of scales being formed at the periphery These scales adhere to the skin by one of their ends A new circle is formed afterwards, separated from the first by a small zone of apparently healthy skin. Thus new



741 Tinea imbricata of the back
*(Trop. Instituut—Amsterdam)*

concentrical circles are successively formed until the lesion is completed with its characteristic aspect.

The occurrence of still more circles is not regular, the evolution becoming more and more delayed, resulting in still wider spaces between the circles. The formation of circles per lesion is limited to at most ten (MANSON, CASTELLANI).

The lesions are usually extremely itchy and the patient finally infects other regions of the body Even the face may become affected, but the

eyebrows eyelashes and the hair remain free The genital organs and the soles of the feet remain unaffected On the contrary lesions may occur in the palms of the hands which assume a keratotic, even fissuring appearance.

The pruritus is more intense in summer when perspiration is abundant and it increases considerably by contact with sea water the ingestion of salty foods (fish and crustaceans) and alcohol.

Tokelau or Tinea imbricata is a purely cutaneous disease, the general condition not being affected except for the feeling of inconvenience because of the pruritus and the repulsive appearance.

CASTELLANI found *eosinophilia* varying from 6–45 % in all cases



742 Tinea Imbricata of the thigh circinated scaling lesions

examined more marked in old than in recent cases The eosinophilia is constant, even in the absence of helminthiasis

Tokelau does not heal spontaneously when not treated it may persist for life

**DIAGNOSIS**

In recent cases when the typical lesion with concentric circles is found diagnosis is easy In old generalized cases diagnosis becomes more difficult owing to the absence of typical lesions, large chronic plaques being formed with abundant scaling In these cases diagnosis is only possible by mycological examination.

Tokelau was for a long time confused with *ichthyosis* When old

lesions of tokelau become keratotic they may indeed resemble ichthyosis, but microscopic examination of the scales may solve the problem.

Differential diagnosis with *pityriasis rubra* is easy as in this case there is a cutaneous hyperaemia and the scales do not contain *T concentricum*

The exfoliative dermatoses are also distinguishable by the absence of parasites in the scales.

*Leprous achromia* may resemble tokelau but in the former there is analgesia and lack of *T concentricum*

Tokelau should also be distinguished from other dermatomycoses, *e g herpes circinatus* and *eczema marginatum* but these fungus diseases do not reveal concentric scale formation and of course mycological examination will show the difference

## THERAPY

Since tokelau or tinea imbricata is a purely local dermatomycosis without any general organic manifestations local antiparasitic agents can be used Before applying any drug however the lesions must be washed with soap and water A daily bath, using soap and sometimes even oil is necessary for the removal of the scales.

Treatment may be with iodine salicylic acid, benzoic acid, resorcinol or chrysarobin.

According to TRIBONDEAU chrysophanic acid is a specific agent for tokelau. It may be used as a 2 per cent. ointment.[1]

JEANSELME recommends the following formula, which is said not to irritate the eyes

| | |
|---|---|
| Chrysophanic acid [1] | 10 g |
| Gutta-percha | 10 g |
| Chloroform | 80 ml |

In widespread cases one should beware of intoxication by chrysophanic acid or chrysarobin which may affect the kidneys.

Recently CASTELLANI successfully used carbol-fuchsin

[1] Since chrysophanic acid is not sufficiently effective and forms chrysarobin, the latter should be prescribed in a 1 to 2 per cent. ointment or tincture made with benzoic acid (See also STRAKOSCH's article in The Arch. of Derm. and Syph. 1944)

| | |
|---|---|
| Basic fuchsin | 1 g |
| Absolute alcohol | 10 ml |
| Dissolve and add | |
| 5 % sol. of phenic acid | 100 ml |
| One hour after add | |
| Boric acid | 1 g |
| Two hours after add | |
| Acetone | 4 ml |
| Three hours after add | |
| Resorcin | 10 g |

The solution should be stored in a dark, well-stoppered bottle and applied once or twice daily for a week

Undecylenic acid is not as effective as the other known agents for the treatment of tokelau

Because tokelau is very resistant to therapy treatment should be continued after the clinical cure of the condition.

## PROPHYLAXIS

Personal hygiene is indispensable for prophylaxis As a general prophylactic measure intensive treatment, as early as possible, is essential to prevent the spread of the disease. Strict sanitary inspection is necessary to prevent the carrying of tokelau to unaffected areas.

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# TINEA VERSICOLOR

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### DEFINITION

Tinea versicolor is a fungus disease of the skin caused by *Malassezia furfur* exclusively localized in the horny layer of the epidermis, without systemic involvement. It is slightly polymorphous in its symptomatology, hardly contagious, easily curable but relapsing. Synonyms are *tinea flava, pityriasis versicolor, body patsy, panu, lota* etc.

### EPIDEMIOLOGY

Tinea versicolor is a widespread affection found all over the world. Its incidence, however, varies extraordinarily between some countries and others. In temperate climates its frequency does not exceed 0.5 per cent. of all skin diseases, while in tropical zones like western Samoa (MARPLES) some 50 per cent. of the natives are affected. ADAMSON and VANBREUSEGHEM have stressed the great frequency of the disease in India, Ceylon and the Belgian Congo.

Only very rarely does the affection occur in infancy; more often than not young adults are involved, while spontaneous recovery invariably follows towards old age, when it is extremely rare.

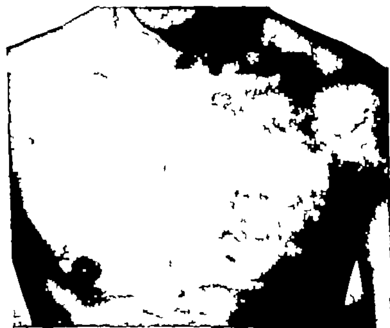
Contagion can rarely be proved. The *incubation period* is about one month (DARIER). The fawn-coloured patches readily lose their colour with frequent recrudescence in a milder form.

There is no doubt that certain climatic conditions are necessary for

the spread of the disease, which explains its varied incidence as between the different countries.

## SYMPTOMATOLOGY IN THE WHITE AND THE COLOURED SKIN

Tinea versicolor is characterized by multiple patches of a yellowish-brown ("café au lait") colour, resembling pigmentation, sometimes surrounded by a slight erythema, and varying as regards intensity of



743 Achromatic type of tinea versicolor in a Javanese.
(*Simons, Amsterdam*).

coloration, as between one case and another, as well as in the same individual, according to the region which is examined and the time of the observation ("versicolor" *i.e.* changing colour). The lesions vary in size between a pinhead and the invasion of large areas of different shapes: annular, discoid, irregular and in rare cases bow- or ring-shaped (UNNA, WOLFF and MULZER). The surface may be a little greasy and sometimes slightly scaly. When the surface is scratched, the

clinical signs are shown more pathognomonically a soft, wrinkled scab may be easily pulled out without causing any pain or bleeding it resembles the shavings falling out when wood is being planed ("*scratch*" or "*copeau*" (*shavings*) *sign*)

The patches of tinea versicolor may be either insignificant and with little colour such as occur after insolation or of the miliary spotted variety (GOUGEROT) or on the contrary they may involve and cover large cutaneous areas. Other cases, again, show a papular (RIETMANN) or a papulo-follicular (EHRMANN VILANOVA) modality and contain,



744 Tinea versicolor achromatic type in the coloured skin.

(*Orig G. Carte-Bele Hernández*)

also in infancy papulo-erythematous, circinate and polycyclic elements which rapidly develop (SABOURAUD)

In many cases the confluence of the lesions gives place to an extensive eruption of a reticular nature

Of great interest, and deserving careful study is the ***achromatic sub-type*** of tinea versicolor in dark skinned patients This may be either primary or secondary when called consecutive achromia parasitaria. It is debatable whether the achromia is due to the direct action of the

parasite on melanogenesis (LIPSCHÜTZ, FINGER, RIEHL, WERTHEIM) or to the interference by the scab which acts as a filter refracting the sun's rays and preventing pigmentation (GOUGEROT and MEYER) or to the whitening of the same scab by the action of the sun (STEIN) Possibly none of these mechanisms is the exclusive cause. (See Volume I page 42 and Fig 20) The true achromatic varieties of tinea versicolor differ from the common form only by the whiteness of the lesions, but the patches have the same configuration, aspect and general distribution

The tinea versicolor patches are usually localized in the upper



745 Scratch or "copeau" (shavings) phenomenon.
(*Siemens-Leyden*)

part of the trunk, both back and front, whence they may spread to the abdomen, groin, armpits, neck, and the proximal segments of both extremities. More rarely they occur on the throat, chin, cheeks (VILANOVA) the hair-covered skin (KELLER, BAER) the palms of the hands (GOUGEROT) and, very atypically on the footsoles (SMITH)

KITTAKOVSKY LEWIS and HOPPER have demonstrated the fluorescence of the tinea versicolor scabs to ultraviolet light. According to CORNBLEET SCHARR and POPPER this is due to the presence of cholesterol crystals in the corneal layer

The disease proceeds without any indisposition but for a rare slight irritation in the initial stages

Heat sweating a rise in the surrounding temperature, dirt and unhygienic conditions are predisposing factors, and the disease is accordingly more frequent in summer and in hot climates. It does not cause allergic cutaneous changes (VILANOVA and CASANOVAS)

## DIRECT EXAMINATION

This is done by washing the scabs with a 10 per cent. potassium iodide solution, or with lactophenol, preferably preceded by aniline staining *Malassezia furfur* was first discovered in 1846 by EICHSTEDT and described by ROBIN in 1853 The organisms have the form of small filaments 2–3 micron in diameter with only a few large ones, between 15



746 Achromatic type of tinea versicolor on sunburned white skin "achromie parasitaire à recrudescence aestivale"

and 40 micron, either separate or continuous some irregularly curved, without any ramification but tending to intermingle and form a dense network. Between the meshes of this network there are irregularly disseminated elements either ovoid, spherical or polygonal, refractive and more difficult to stain they resemble blastospores, have a diameter from 3 to 8 micron, and in some cases appear to be in the process germination they nearly always form into clusters of between 10 and 30 elements. It has not, so far been possible to determine the precise relationship between these elements and the Malassezia furfur filaments

**CULTURE**

It is generally considered that Malassezia furfur cannot be cultivated although numerous authors have reported success in obtaining a culture (VOERNEL, SCHMITTER, PLAUT and GRÜTZ, MACLEOD and KOTLIAR, NICOLAU and GASTON OTA and NICOLLE, MATZENAUER, RUETE, KAMBAYASHI, MARQUARDT and MOORE) all these authors reports agree in that they describe the cultures obtained as very small, moist and sticky shiny and yellowish they disagree, however as to their form which—all according to the author—was either round or rounded long and thin, or cratenform.

According to KAMBAYASHI (1932) the microscopic picture of the



47 Abundance of mycelial elements in direct examination. A few o oid cells are visible.

spores in the glucose-peptone-agar medium is almost ovoid or rather longer there are about 5 or 6 micron, while those in the liquid media are almost spherical. There are also short hyphae with either pointed or rounded extremities, between 2.4 and 2.6 micron in diameter and either straight or partly curved In older cultures there are larger hyphae with many ramifications, with short lateral branches ending in slightly differentiated conidiophores. In some cases there are conidia in short chains of 2 or 3 cellules, between 3 and 6 per 4 micron.

INOCULATION

With the colonies obtained by the various investigators practically no successful inoculation has ever been made either in animals or in man. GOUGEROT reports having obtained a positive result with re inoculation of subjects with the same parasites. Re-inoculation of achromatic patches with tinea versicolor achromatica parasites appears to be negative, which seems to indicate the presence of some local immunizator

INTRADERMAL TESTS

In all cases investigated by ourselves, reactions to both trichophytin and levurin were invariably negative.



748 Tinea versicolor Blastophore-like elements.

HISTOPATHOLOGY

The skin is normal nevertheless, between the corneum and the stratum granulosum there exists a virtual fissure or faulty adherence which histological expedients are able to demonstrate

The hair is never infected. Malassezia furfur infects for preference the superficial strata of the skin, discharging the mycelial filaments more deeply and the ovoid and levuriform elements on the surface. "The mycelia may dip down into the prickle cell layer or even into the rete" (SUTTON and SUTTON)

**DIAGNOSIS**

The diagnosis is easy and evident in typical cases seen in Europe and North Africa. In all doubtful cases investigation of the parasite is absolutely essential. The differential diagnosis has to do, first and fore most, with *erythrasma* particularly as regards the localizations in the armpits and groins (JESIONEK) In erythrasma, however the coloration is more intense in almost every case there is a large homogeneous intertriginous patch in the area of contact there is more apparent



49 "Panu" or achromia parasitaria from tinea versicolor in a Javanese.

*(Siemens–Amsterdam)*



750 Consecutive achromia is not only seen in tinea versicolor yaws, etc. This is a case in eczema in a Javanese

desquamation new points of invasion arise close to the main affected region and only rarely spread (NIKOLOWSKY and STABLE) the scales are nonfluorescent to Wood's light (ORMSBY and MONTGOMERY), and, finally they do not contain Malassezia furfur *Pityriasis rosea* (GIBERT) is characterized by its eruptive polymorphism, the presence of ring

shaped patches, the erythematous colour of the macules and its spontaneous cure within a few weeks. Confusion with *naevus pigmentosus* ("taches hépathiques") is easily avoided by bearing in mind that these patches do not scale and do not spread. In the case of *vitiligo* and *leukoderma* confusion is possible only with tinea achromatica they are distinguished, however from the latter in that they are not squamous have their own distinct localization, frequently show perivitiliginous melanoderma, and have very irregularly shaped patches *Syphilitic exanthemata* particularly the leukomelanodermal ones rarely lead to confusion because of their localization and the absence of any clear delimitation between the pigmented and the hypochromic patches.



751 Tinea versicolor fungous elements in the corneal layer loosened because of shaving phenomenon

In tropical and subtropical zones the number of epidermic mycoses which may give rise to confusion with tinea versicolor is very large. Most of them have been insufficiently studied, and there is no doubt that much still remains to be known and described. (See also Fig 113 114 213 (Vol 1) and the section on porphyria )

The most interesting is *tinea flava* (CASTELLANI and CHALMERS) also called Pityriasis versicolor flava, or tinea rosea (CASTELLANI), very often localized in the face and attributed to Malassezia

tropica. Nevertheless GOUGEROT JOYEUX and VUILLEMIN identify the organism with Malassezia furfur and consider tinea flava to be a mere variety of tinea versicolor

Other parasitic achromias to be chiefly taken into account in establishing a diagnosis are, *tinea imbricata* or *Tokelau ringworm* caused by Endodermophyton concentricum castellani *body-pety* of Madagascar caused by Hormodendron fontoynonti *tinea alba* provoked by Epidermophyton rubrum castellani and Atrichophyton macfadyeni *tinea nigra* due to Gladosporium mansoni (CASTELLANI) further the *parasitic achromias* caused by Aspergillaceae (PARDO CASTELLO and DOMINGUEZ) those provoked by intermediary forms Malassezia furfur and Hormodendron (PARREIRAS HORTA) in Brazil, and finally the alleged treponematosis *carate* (mal del pinto spotted sickness) For *tinea albigena* see Chapter 59

#### THERAPY

Fungicides and exfoliatives will soon eliminate the eruption. A 1 per cent. alcoholic iodine solution, 5–10 per cent. sulphur ointments, salicylic or benzoic acid and napthol are equally recommendable. Undecylenic acid might shorten the rather long course of some cases (VILANOVA and CARDENAL) The concentration of the remedies employed must depend on the areas that are affected and on the tolerance of the skin Daily washing is essential. As to repigmentation of the achromic spots by exposure to the sun one should bear in mind that only the surrounding skin may become darker thus making the achromia still more distinct from the normal skin (Achromie parasitaire *à recrudescence estivale* JEANSELME). For this reason one should investigate whether the achromic skin is again prone to pigmentation by exposing one lesion first. In any case the surrounding skin should be covered by a sunprotecting cream.

In order to prevent relapses it is absolutely necessary to eliminate the parasites from the skin and from bed-linen and clothes, by thorough disinfection. For this purpose treatment should be continued for some weeks after the cure has been apparently completed.

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CHAPTER 58

# TINEA NIGRA

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## DEFINITION

Tinea nigra is a contagious, inoculable and autoinoculable dermatomycosis which is caused by two fungi Cladosporium mansoni and Cladosporium wernecki It is characterized, from the clinical point of view by its black or brown coloration and by its sites of preference on the trunk and neck (Orient) and on the palmar region (Brazil and Cuba) the disease may however occur on any part of the cutaneous tegument.

Tinea nigra is also known as keratomycosis, keratomycosis nigricans palmaris, cladosporiosis epidermica, pityriasis nigra and microsporosis nigra. The denominations keratomycosis or keratomycosis nigricans palmaris should not be adopted, because there are extrapalmar localizations of the disease to be met with in the East and in Brazil [1]

## HISTORY

The first reference to tinea nigra was made by MANSON in 1872, in South China.

Besides this the term keratomycosis may cause confusion with corneal ocular mycoses. The most suitable name would be cladosporiosis epidermica, but this name is inconvenient, as it refers to the causal agent which may in the future receive a different mycologic classification.

The name pityriasis nigra is unsuitable because it is liable to be confused with pityriasis versicolor

In 1905 CASTELLANI rediscovered the disease, in Ceylon, and isolated its causal agent. As regards the disease which CERQUEIRA in 1891 in Bahia (Brazil) called keratomycosis nigricans palmaris, his object was to individualize a morbid entity observed by him which produced a black coloration and was localized on the palms.

SILVA affirmed that in a report of CASTELLANI and CHALMERS they verified, by examining the China Maritime Customs House Medical Reports, that the disease described by MANSON was not tinea nigra but was perhaps pityriasis versicolor If this is so then CERQUEIRA was the pioneer in the study of this mycosis.

In 1921 RAMOS E SILVA in Rio de Janeiro reported another case in which PARREIRAS HORTA isolated a fungus which he called C werneckii.

#### EPIDEMIOLOGY

The disease is confined to the East and to the Americas. In the East it has been reported from Ceylon, India, Burma, South China, Java, Sumatra and Bangka, Timor and Borneo In Brazil it has been met with in the states of Bahia, Rio de Janeiro and Minas Geraes PARDO CASTELLÓ has reported a case in Cuba

#### SYMPTOMATOLOGY

The clinical symptoms of tinea nigra are nearly identical in the Western and Eastern hemispheres In the East the favourite sites are the neck and upper part of the thorax the disease, however may affect any part of the integument, the face being least often affected. In the Western hemisphere, the disease in the great majority of cases is found in the palmar regions. The soles, like the other parts of the tegument, are unaffected There is no modification of sweating in the palmar regions.

SILVA affirmed that the most frequent sites in cases in Brazil are the palms the sides of the fingers the wrists, the interdigital spaces and the cubital border

The disease is manifested by the appearance of black or brown spots The primary lesions coalesce later forming irregular polycyclic patches of varying size which are smooth and slightly or not at all itchy with moderately raised edges. Neither erythema nor any inflam-

matory phenomenon is noticed. PARDO CASTELLÓ made a good comparison between the colour of tinea nigra and that of India ink.

RIETMANN stated that no scales vesicles or raised edges are observed, the patches being absolutely level but at times rough to the touch. SILVA was of the opinion that the patches fade or disappear spontaneously to reappear and increase later

LANGERON and HORTA expressed the opinion that the parasites of oriental tinea nigra and so-called keratosis nigricans palmaris are different, their opinion being based on the appearance of the parasites in the scales and in cultures.

In Brazil, SILVA was the first to admit the clinical identity of the two mycoses.



52 Tinea nigra india ink-coloured patches caused by Cladosporium mansoni or C. werneckii.

The oriental mycosis is localized preferentially on the neck and upper part of the thorax, while the American form of the disease nearly always attacks the palmar regions and the palmar surface of the fingers. It must be pointed out, however that in Ceylon C STELL [illegible] observed palmar localization while in Brazil R [illegible] S [illegible] and SILVA ha[illegible] observed eruptions affecting the neck.

LANGERON stated the belief that the two diseases are different, because tinea nigra of the palms seems to be an exclusively tropical or even exclusively Brazilian disease, occurring generally on the palms and rarely on other parts of the skin. There is also the fact that the type of cladosporium which is the causal agent is different from that which produces tinea nigra.

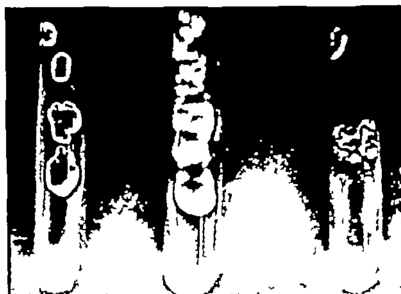
LANGERON therefore concluded that the two epidermomycoses are definitely differentiated by their clinical, geographic and aetiologic features. As regards

localization, we have seen that both dermatoses may affect the hands and the neck indifferently As regards geographic distribution it has been shown that both diseases are met with in tropical or subtropical regions. As regards the parasites, these differ only in species, for both belong to the genus Cladosporium.

Our belief being based on these facts we are of the same opinion as SILVA, viz., that the two diseases are identical.

## MYCOLOGY

Tinea nigra is caused by the action of C. mansoni in the East and by C. wernecki in the Americas AREA LEÃO, CURY and FERREIRO FILHO



753 Cladosporium wernecki, mixed type culture (glabrocerebriform, nine days, Sabouraud's maltose-agar medium) culture of cerebriform type, nine days in Sabouraud's maltose-agar medium, and culture, seventy-four days, in Sabouraud's maltose agar Note the absorption of the dawn.

have tried to reproduce the disease in human beings and in animals (guinea pigs, rabbits and rats), without success

*Macroscopic and Microscopic Aspects of the Cultures* —1 Sabouraud's Maltose Agar On the third day we noted the appearance of the first hyphae On the fourth day the first ramifications appeared. On the fifth day there appeared macroscopically small dark points in the scattered scales, while in the colonies mentioned the branchings

became more numerous as development proceeded. On the sixth day the appearance of small, dark, more spherical colonies was already noted macroscopically On the eleventh day the colonies measured 2 to 4 mm in diameter Some of these had a mamilliform central spot, dull greenish black, surrounded by a border of short, velvety grayish green hairs measuring sometimes 1 mm in width. In other colonies the central zone was wider, black, shining, smooth and moist, with mamillae separated by grooves there was the same border previously described, of the same colour and aspect but ex tremely narrow On the twenty third day some colonies measured 1 4 cm in diameter with a central umbilication measuring 0 1 cm in diameter and of a slightly greenish gray This was followed by another which was dark gray glabrous, 0.3 to 0 4 cm in diameter with a border of the same colour as the central zone, filamentous satiny looking, 0 15 to 0.2 cm in width and free from radiations. Such colonies we shall term *cespitose* (Fig 753 second culture) Other colonies showed a central black umbilication, smooth and brilliant, surrounded by a filamentous zone. Outside this there was another border 0.25 to 0 15 cm in width, rather dark and almost glabrous In the former type filamentous forms were predominant, while in the latter the yeast forms were commonest. These data refer to cultures made from scales

Da Fonseca and D Rosa stated that in Sabouraud s maltose medium the cultures show only greenish brown yeast forms our cultures however, which were closely observed from the start, contained simple hyphae and ramifications, with complete absence of yeast forms. Such forms appear from the fourth to the sixth day however as isolated islets in certain parts of the scattered scales, giving the impression of a mixed culture.

Cultures on Corn Meal Agar (Emmons method) In a medium of corn meal agar also the two types can be separated, one glabrous and the other cespitose.

1 The colonies look smooth, black and somewhat shiny and are surrounded by short mycelial grayish filaments. They secrete a dark pigment.

2 The colonies are lighter in colour deep olive in the central part and surrounded by a finely radiated border dark yellowish olive in

colour; only traces of yellowish olive pigment are diffused in the medium.

The left hand tube represents a culture of mixed type, glabrous-cespitose, in Sabouraud's maltose medium.

DODGE and NEGRONI classified the causal agents of the two forms of tinea nigra—the American and the Asiatic—as belonging to the genus Dematium Persoon, 1497. LANGERON and BRUMPT classified the agent of Asiatic tinea nigra as genus Torula Persoon, 1796 while PINOY in 1912, classified it as Cladosporium Link, 1816. In spite of this, LANGERON and BRUMPT classified the agent of American tinea nigra as Cladosporium. These divergencies are probably related to the forms present in the cultures of the fungus which would specially draw the attention of these mycologists.

We deduce that DODGE and NEGRONI were impressed by the conidial system, that is, spherical or ovoid conidia, which are unicellular, dark coloured and sometimes joined by short, intermediate elements. LANGERON and BRUMPT however were impressed by the conidium-bearing branches which are short or just distinguishable from the conidia. PINOY was impressed by the conidiophores almost erect, branched and interlaced, frequently cespitose and olive coloured.

We conclude that there is a specific difference between C. mansoni and C. werneckii.

In the former, as a matter of fact, in the conidial apparatus, besides the predominant fuliginous spherical forms there are ovoid hyaline forms which, in our opinion, are the youngest forms. Among the predominant forms there are some with a rough outer surface and others with one septum of a more or less fuliginous colour and of varying dimensions.

POLLACCI and NANNIZZI stated that C. mansoni "examined under the microscope is seen to consist of a dense interlaced mass of brown hyphae, with short segments, of varying shape, frequently oval or round and sometimes divided into spherical arthrospores 8 to 10 microns in diameter generally containing a large oily drop of liquid. More rarely on the surface of the colonies, especially in adult ones, there appear olive-coloured hyphae with few ramifications, some 0.8 to 1 micron and sterile and others 2 to 2.5 microns wide and terminated by oval or elliptic conidia."

The preparation which we had the opportunity of examining accompanied the volume referred to as that by POLLACCI and NANNIZZI.

*Comparison of Cladosporium werneckii with Cladosporium mansoni*

| Cladosporium werneckii, Parreiras Horta, 1921 | Cladosporium mansoni, Pinoy 1912 (According to Pollacci and Nannizzi and Colleagues) |
|---|---|
| **In the Lesions** | |
| Mycelial articles | |
| Simple or branched | Not branched |
| Spores | |
| Round or ovoid | 5 to 10 microns, round |
| Arrangement | |
| In groups, branched or not, pigmented or hyalin, curved | In groups, unbranched, curved like banana |
| **Cultures** | |
| Optimum temperature | |
| 18 to 25 C (surroundings) | 30 to 32° C |
| First appearance of colonies | |
| Macroscopic 5 to 6 days | 2 to 4 days |
| Two types | |
| 1 Hemispherical colonies, doughy shiny black non-adherent to medium | Hemispherical, rounded, greenish, then black with greenish delicate fibrillae irradiating toward the periphery these are at first isolated but later become confluent to form a black shiny plaque, penetrating deeply into the substratum |
| 2. Cespitose, olive-gray strongly adherent to medium both when they become old get dull, with an irregular smooth black surface strongly adherent to the substratum | |
| Microscopically | |
| Predominance of yeast forms (conidia) in the first type and of hyphae in the second the latter are septate, now in short segments, now in long ones, arranged in arthrospores or not. | The hyphae are brown, with short segments of varying shape, oval or round and divided into spherical arthrospores |
| Conidia | |
| Oval or elliptic ones predominate they are rarely spherical, fuliginous or hyalin, either nonseptate or having up to 3 septa the unseptate being predominant | The spherical fuliginous types predominate, ovoid and hyalin. |
| Hyphae | |
| Sterile | Sterile forms |
| Fertile 2.9 to 5.8 microns in width | Fructifying forms 2 to 2.5 microns wide |
| Type of fructification | |
| Acrogenous and pleurogenous (sympodial) | Acrogenous and pleurogenous (sympodial?) |

Our studies have enabled us not only to confirm the conclusion of the majority of authors but also to adduce new facts which lead us to place the causal agents of tinea nigra in the genus Cladosporium.

In view of the foregoing we conclude that the causal agent of Ameri

can tinea nigra should be considered as belonging to the genus Cladosporium and that the species C. werneckii Parreiras Horta, 1921 is legitimate, having the following synonyms

Montoyella nigra, Castellani and Chalmers, 1913
Cladosporium sp., Rietmann, 1930
Cardosporium sp., Sartory Sartory Rietmann and Meyer 1930
Dematium werneckii, Dodge, 1935
Cladosporium Rietmann, Sartory 1935
Cladosporium tropicalis, Sartory Sartory Meyer and Weiss, 1935

DODGE stated his belief that the black form of caraté or pinta, seen in certain South American countries, is identical with tinea nigra, and at the end of page 567 in his "Medical Mycology DODGE described Dematium werneckii (Parreiras Horta) The organism usually isolated from black caraté or pinta in South America." This condition now has been proved to be due to treponema, its specific agent being Treponema carateum Brumpt, 1939

## HISTOLOGY

The fragment of skin had a thick corneal layer at the level of the more superficial strata, in which mycelial fragments and spores of a light brown colour were seen the hyphae were short, thick and septate and straight or curved, a terminal spore being seen in some of them. The presence of the fungus had brought about cleavage of the corneal layers At times some filaments were met with, deeper in the corneal layer, but not as deep as the stratum lucidum. In one of the sections examined a small area of parakeratosis was seen, in which, however there were no fungi. There were no modifications in the other epidermal layers The changes met with in the derma were slight at the level of the papillary body two small foci of lymphocytic infiltration were seen, and there was an increase of connective tissue cells round an arteriole in the middle derma (JUNQUEIRA)

## DIAGNOSIS

The disease must be differentiated from pityriasis versicolor epidermic blastomycosis, pinta or caraté tinea nigrodermata (Trichophyton ceylonense) chloasma, liver spots melanoderma of Addison's disease and dermatitis due to Ficus caricaca (fig tree)

### THERAPY

SILVA stated that he cured all his patients with an ointment composed of salicylic acid, benzoic acid, sulphur, resorcinal and petrolatum.

Our patient was radically cured by use of the following formula

| | |
|---|---|
| Salicylic acid | 1 part |
| Metallic iodine | 1 part |
| 90 per cent. alcohol | 100 parts |

The following formula is also recommended 2 to 3 per cent. alcoholic solution of salicylic acid and 10 to 20 per cent. ointment of benzoic acid, sulphur and resorcinol. Undecylenic acid, propionic acid ointments are popular today

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CHAPTER 59

# So-called
# TINEA ALBIGENA

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Amsterdam

## HISTORY AND SYMPTOMATOLOGY

NIEUWENHUIS reported on a newly discovered mycosis at the first Congress of Biology and Medicine in Java (1903); he later published several papers on his discovery (1904, 1908, 1908). He recorded that this disease of the skin (which he named tinea albigena, because of its most striking symptom—lasting discoloration) bears a certain resemblance to tinea circinata and tinea imbricata, but greatly differs from these dermatoses by being localized chiefly on the palms of the hands and the soles of the feet, as well as by the strong depigmentation which eventually develops. Onset of the disease is manifested by a violently itching papilla from which a vesicle develops; this initially contains a clear fluid, afterwards turning purulent. New vesicles appear at random in the vicinity (not in concentric circles as with tinea circinata and tinea imbricata).

NIEUWENHUIS for the most part described attacks on the feet. It is possible that fissures may appear in the soles of the feet and cause a secondary infection. According to NIEUWENHUIS, therefore, tinea albigena is a surface dermatosis, to be considered as belonging to the same group of parasitary dermatoses as herpes tonsurans, *i.e.*, caused by *Trichophyton*.

"The disease only attacks the surface," NIEUWENHUIS goes on. "This is proved by the fact that the pigment disappears." He even speaks of "pigmentary atrophy." It takes many years before the discoloration becomes very marked, but it may lead to complete absence of pigment; this is only found in adults, however. NIEUWENHUIS is of the opinion that a more severe, deeply seated inflammation is out of the question. Although tinea albigena occurs mainly on the palms of the hands and the soles of the feet, the forearms and legs may also be involved. In the latter case the process develops in a manner similar to chronic eczema: a thickened, creased, superficially scaling skin

which looks grey from a distance as if it were powdered with flour; here also discolouration may develop.

NIEUWENHUIS once observed the disease in the groin and once on the breast and the trunk. Often, though not always, the nails are also involved; the nail beds may shrivel and leave thin, irregularly formed nails. Tinea albigena shows a very distinct symmetry which, according to older conceptions, indicates the influence of internal and nervous factors. The strong therapeutic action of several parasitical remedies, however, on the depigmentation as well as the finding of festering fungi in the epidermis, induced NIEUWENHUIS to consider the latter as being the cause of the infection. He



754. Tinea albigena according to NIEUWENHUIS. In the present author's opinion pinta or vitiligo being superpened by epidermophytosis, the fungi (and their pleomorphism) of which had not been recognized by the discoverer.

was of the opinion that the symmetry was probably due to physical and chemical properties of the principal localizations of the infection.

Microscopically NIEUWENHUIS discovered numerous threads of mycelium in the scales of the hands, the edges of the feet and the nails.

Whereas in tinea imbricata the mycelium is composed of several somewhat rounded cells, causing it to show indentations, the densely matted hyphae of tinea albigena do not contain separate cells, but are smooth with only ill-defined articulations. There exist other forms that look like a widely meshed network and are composed of rows of oval cells with a strongly granular content, interspersed with cells of less regular structure.

No formation of spores was observed. NIEUWENHUIS admitted that the

fungus he discovered possesses too few characteristics to enable him to distinguish it from other forms of tinea. *He emphasized that his differential diagnosis depended solely on clinical symptoms and on the presence of fungi in the pathological products* Tinea albigena differs from other pigment-diseases by its marked loss of pigment. If the infection does not commence on the palms of the hands or the soles of the feet tinea albigena may be excluded.

Four years after his first publication NIEUWENHUIS recorded that further microscopical research had yielded little of interest, except the discovery of spore formation in the nails of a patient suffering from onychomycosis. It concerned some rounded-oval spores, situated next to or at the end of the hyphae, several of which were reddish-brown in colour He succeeded in



755 Characteristic triangular leukoderma in pinta. Note rest of pigment in the leukoderm.

*(Pardo Castello–Havana)*

growing this fungus and in causing onychomycosis by inoculation with the culture from this patient he again isolated the same fungus. NIEUWENHUIS effected 13 inoculations with his initial strain, dating from April 1903 For a long time the fungus did not produce conidia until suddenly *a culture on an agar medium developed a fairly long, white string of air-hyphae which finally covered the whole of the mycelium The formation of conidia was observed in this air-mycelium in the most primitive forms (N B )*

NIEUWENHUIS would not have differentiated the disease from mal de los pintos had not SCHÜFFNER written that this mal de los pintos may also be found in the Straits-Settlements. The differential diagnosis with pinta was based

on the fact that notwithstanding both infections being caused by fungi (!) *mal de los pintos never invades the palms of the hands or the soles of the feet* even after a duration of years and when covering great parts of the body! Moreover several colours may be observed in mal de los pintos.

The disease also differs from vitiligo as the spots of tinea albigena have no dark edge and the localization is different from that of vitiligo. Furthermore, it must be differentiated from leprosy in which the spots are analgesic. Panu or tinea versicolor (achromia parasitaria) is another fungus disease that causes leucoderma, but it differs so greatly from tinea albigena that we need not labour the point.

The disease may be differentiated from albinismus circumscriptus by the localization of the latter. NAUCK (1932) therefore suggested that the cases of albinismus in Africa, described by PLEHN, were really tinea albigena.

NIEUWENHUIS seems to have overlooked the fact that he was probably observing pleomorphism or an airborne contamination. The definition of pleomorphism comprises loss of characteristic properties, limited or scarce production of spores and an air mycelium. NIEUWENHUIS' *findings are the prototype of pleomorphism*.

As only the onychomycosis of this dermatosis is said to survive in the Netherlands NIEUWENHUIS tried to infect a sound nail with the fungus. He seems to have succeeded after covering the toe with sterile gauze and oiled paper: within a few days the toe started to itch. Eight months later the toe nail was discoloured and looked very much like the original onychomycosis. The nail showed a white air mycelium (as pleomorphism is irreversible).

He concluded (a) that the culture is most clearly characterized by the different forms originating from media of different composition and (b) that when comparing two fungi, care should be taken that the media on which they are grown are identical. NIEUWENHUIS concluded that this fungus belonged to *Trichophyton* and he named it *Trichophyton albiscicans*. He published a summary of his two papers in 1908, repeating his differential diagnosis with pinta and *again pointing out that in pinta the palms of the hands and soles of the feet are not involved*. This publication induced PLEHN to insert a picture of a Negro with advanced tinea albigena in MENSE's *Handbuch für Tropenkrankheiten* (1924).

NAUCK (1932) devoted a whole chapter to tinea albigena in JADASSOHN's *Handbuch für Haut- und Geschlechtskrankheiten*. He wrote that tinea albigena is probably found in the whole of South-East Asia and that JEANSELME described it in Siam as khi huen. This khi huen, however, is said to be often attended by arthralgia. Some of the cases of albinismus partialis described by PLEHN in Africa were really tinea albigena. NAUCK copied the description of NIEUWENHUIS, as KAYSER did in his "Lectures on tropical dermatoses".

## MYCOLOGY

OTA (1925) examined the cultures of NIEUWENHUIS and was of the opinion that the fungus was a *Glenospora* he therefore named it *Glenospora albiciscans* NIEUWENHUIS-OTA. In BERCOVITZ *Clinical Tropical Medicine* the fungus is named *Alternaria albiciscans* NIEUWENHUIS-DODGE (1935). (DODGE postulated that the fungus of black pinta was identical with *Dematium* or *Cladosporium werneckii* of tinea nigra.)

NAUCK pointed out that the fungus is also a saprophyte found on plants and that infection from man to man has not yet been proved, notwithstanding the experiments of NIEUWENHUIS.

## DIAGNOSIS

As regards differential diagnosis, NAUCK said that the lesions of mal de los pintos (carate) are often coloured in the early stage of the disease and that they do not occur on the palms of the hands or the soles of the feet. Though a number of publications on tropical medicine omit reference to tinea albigena it is mentioned in JOYEUX (1945) *Précis de Médecine coloniale* BERCOVITZ (1944) *Clinical Tropical Medicine* and in the Dutch textbook on skin diseases by CAROL (1948).

## COMMENT

Nowhere did I read any criticism of NIEUWENHUIS researches, nor was the existence of the disease as such doubted. Descriptions of the disease (all based on NIEUWENHUIS data except for OTA's fungus examination, no other research was made) contain four factors:

(*a*) The disease has two stages an early stage of papules and vesicles, appearing for the most part on the feet, and a late one after many years of depigmentation. *It was never reported that* NIEUWENHUIS *observed both stages in the same patient or that he found the fungus in the depigmented areas neither did he succeed in experimentally provoking this depigmentation*

(*b*) For NIEUWENHUIS the most important differential diagnosis with pinta was the localization of tinea albigena on the palms of the hands and the soles of the feet, where pinta was said never to be present!

(*c*) NIEUWENHUIS described the morbigenous organism as a fungus with mycelium threads that were not indented and only indistinctly segmented and which originally did not appear to form spores spore formation was seen later on in the nails a long white string of air hyphae covering the mycelium. He admitted in his first publication that this fungus had few characteristics and did not suggest the presence of pleomorphism.

(*d*) The fungus (which NIEUWENHUIS considered as being a *Trichophyton* but which OTA classified among *Glenospora* and DODGE among *Alternaria*) was cultivated from vesicles under the soles of the feet.

Inoculations of the (or one of the) ocrchomycetous fungi again caused ocrchomycosis. This inoculation was practised in the Netherlands using an ocrchomycetous fungus which was taken to this country; the experimental toe was isolated with sterile gauze and oiled paper.

In this respect I want to point out that ZIEMANN described a disease called *ma-ang* which he observed in the Cameroons (1905). I will refrain from verbally quoting ZIEMANN. I only wish to point out that he spoke of "bright yellow-reddish spots" on the inner and under sides of the hands and feet. The discolouration was mostly whitish. The disease started between the 10th and 15th year of age and was symmetrical. The process was chronic.

ZIEMANN considered that both the inner and outer sides were involved. The such discolouration was generally limited to hands and feet, while spots were sometimes found on the wrists and the legs. The population considered it to be an infectious disease. ZIEMANN did not succeed in demonstrating the pathogenic organism. He differentiated the disease from leprosy, vitiligo, etc., and pointed out that in contradistinction to pinta, the latter caused a non-symmetrical discolouration in which, moreover, several other shades of colour may be seen and does not involve the palms of the hands or the soles of the feet.

Discussing the four factors, I will start with (*b*), as (*a*) may better be considered with (*c*) and (*d*). It was stated sub (*b*) that tinea albigena may be differentiated from pinta, as the former is restricted to palms of the hands and soles of the feet, while in the latter these parts are not involved. NATTER says this on page 254 of his *Handbuch*. On pages 317 and 325, however, he published photographs of patients in whom the palms of the hands and soles of the feet were positively involved. In his description of pinta, written before the treponema which causes this disease had been discovered, NATTER gives the following details: long, ramified, mycelium threads may be observed between the epithelial cells at the ends of which fructifying organs may occasionally be seen. In other instances mycelium threads only are found with some spores scattered at random and without fructifying organs. These fungi were very varied — *Aspergillus*, *Penicillium*, *Mucor*, *Monotospora* etc. Often, no fungus at all was observed.

We know now that the fungi found in pinta do not cause the disease; pinta is a treponematosis.

Frambesia [illegible] may also exhibit symptoms resembling pinta. The *Handbuch der Haut- und Geschlechtskrankheiten* 193[illegible], which quotes NOTHNAGEL [illegible] [illegible] reproduces a photograph showing depigmentation [illegible] the palms of the hands in yaws (page 23). On page 24 we read that according [illegible] is a remarkable depigmentation [illegible] [illegible] found. BUTLER on page 24 declares that the discolouration is [illegible] dark brown [illegible]. And on page 25 we read "BUTLER as well as [illegible] emphasizes the resemblance with tinea albigena NOTHNAGEL"

In more recent literature [illegible] discolourations are found in yaws as well as in pinta.

There are no recent publications on tinea albigena, except those in which the

findings of NIEUWENHUIS are simply copied. I have been unable to trace any reference concerning an examination of tinea albigena except that of the fungus research by OTA (1935) and the new classification by DODGE (1935) nor is there any paper in which the existence of the disease is doubted or refuted. Tinea albigena thus still exists even if only by the grace of tradition.

Before discussing the causative agent of tinea albigena and the factors sub (a) (c) and (d) it would be interesting to describe the fungus found in epidermophytosis. A great variety of names have been used for it in mycology (let alone the numerous synonyms of the disease itself in the tropics).

A study of the description of *Epidermophyton floccosum* in the *Manual of Clinical Mycology* (CONANT et al 1947) will show it to bear a marked resemblance to the causative agent of tinea albigena. CONANT wrote 'In the beginning the culture is white and granular with a small central bunch of mycelia later on the growth is luxuriant, powdered with many radial folds, and greenish-yellow in colour White, sterile, pleomorphous air-mycelium hyphae develop in about three weeks and cover the culture SABOURAUD and CASTELLANI named the fungus *Trichophyton*

Thus, we find that the description of the fungus, which according to NIEUWENHUIS 'possessed few characteristics is identical with that of the fungus of epidermophytosis the statement about air-hyphae answers to the phenomenon described (since SABOURAUD) as pleomorphism. This is the state in which cultures lose their characteristic aspect and develop into a sterile string (LANGERON) Not all fungi exhibit pleomorphism, but *Epidermophyton* does.

The terminology of DODGE is only a modernization of VUILLEMIN's nomenclature (1911). VUILLEMIN described aleuriospores as "those spores that are no longer chlamydospores and have not yet become conidia" NIEUWENHUIS observed "formation of conidia in the most primitiv forms"!

The foregoing led me to conclude that

(a) NIEUWENHUIS was mistaken in seperating tinea albigena from pinta or vitiligo on the strength of the assertion that pinta does not affect the palms of the hands or the soles of the feet. (b) He demonstrated fungi that are not specific and that are also found in epidermophytosis. (c) He described pleomorphism as a characteristic feature and (d) his experiments with inoculation did not constitute proof. (e) He found fungi that were isolated from vesicles on the soles of the feet and around which no achromia had generally occurred

Nowhere in the literature can NIEUWENHUIS' findings be confirmed, but his wrong differential diagnosis has always been copied [1]

After the publication of my article on this subject, LANGERON (January 29th 1950) wrote the following „Bien que je n'en aie jamais vu de cas, j'ai été amené à en publier en 1936 une petite monographie dans la Nouvelle pratique dermatologique. J'ai utilisé la très belle illustration de Nieuwenhuis et, pour la mycologie, j'ai dû me contenter de notions classiques mais imprécises et peu satisfaisantes"

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ZIEMANN, *See* NAUCK

CHAPTER 60

# DERMATOPHYTIDS

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## INTRODUCTION

It is well known that secondary allergic eruptions may occur in connection with fungous infections of the skin. The term "*dermatophytid*" first suggested by WILLIAMS, is used here to designate such cutaneous manifestations regardless of whether the infecting organism is a trichophyton, epidermophyton, microsporon, or monilia. Some authors speak of trichophytid, epidermophytid, etc. where the dermatophytid (generic term) is known or suspected to be caused by a trichophyton, epidermophyton, etc.

Dermatophytids appear in specifically altered skin as a result of a haematogenous dissemination of fungi and/or their allergenic products. Following the appearance of the primary infection, the entire skin may become sensitized. At a later period, either spontaneously or due to irritation of the primary lesion (trauma, chemical, X-ray or after injection of trichophytin) there is an outpouring of fungi and/or their products into the blood stream. On reaching the already sensitized skin, the fungi are quickly destroyed but their products (inherent, or of the destruction) may be provocative of "*ids*". Fungi are rarely found in the secondary lesions. There is a positive tuberculin type reaction to an intracutaneous injection of fungous extracts (trichophytin) when dermatophytids are present. Excluding extraneous complicating factors, dermatophytids disappear after the primary focus has been eradicated.

In 1911 JADASSOHN in a discussion of BLOCH'S paper on trichophy

tosis, described several cases of kerion in which spiny lichenoid papules were scattered over the trunk. He referred to this eruption as *lichen trichophyticus*. He was the first to note the connection between the secondary eruption and the primary fungous infection. JADASSOHN believed that an allergic status was indispensable for the occurrence of dermatophytids and called the secondary eruption a hypersensitivity reaction. The earliest dermatophytids reported were those seen in connection with deep trichophyton infections. Later they were observed in cases of favus and in microsporon, epidermophyton and monilia infections. WILLIAMS proposed the hypothesis that some of the dyshidrotic eruptions of the hands were secondary to fungous foci on



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the feet. BLOCH believed that these eruptions on the hands were "ids" and were related to the fungous infection on the feet in the same manner that lichen trichophyticus was related to kerion. The status of these vesicular eruptions of the hands as dermatophytids was established by the work of BLOCH, JADASSOHN and his school, JADASSOHN Jr., PECK, and SULZBERGER. Dermatophytids secondary to foci of infection with monilia albicans have been reported by RAVAUT and RAMEL (*levurids*) and by HOPKINS (*monilids* [1]).

See also Chapters 65, 92 and 93

**PATHOGENESIS**

Experimental and clinical findings have supported the concept of dermatophytids as allergic manifestations. JADASSOHN Jr and SULZBERGER, after cutaneous inoculation of guinea pigs with Tr. quinckeanum, observed two distinct periods of invasion of the fungi into the blood stream of the infected animal. The first occurred within 48 hours and the second occurred 10 to 12 days after the inoculation. The latter coincided with the skin infection in the guinea pig. According to SULZBERGER, the second period of invasion corresponds with the usual time of appearance of dermatophytids in deep inflammatory fungous infections. BLOCH demonstrated by skin inoculations of animals the fact that from the 10th to the 20th day after the first inoculations, and later there is an altered reaction of the skin to fungous reinoculations in the sense of KOCH's Fundamental Phenomenon. SAEVES and KOGOJ inoculated guinea pigs intravenously with fungi and produced skin lesions which contained the fungi. A second inoculation showed an altered capacity of the skin to react with lesions appearing earlier and disappearing more rapidly.

That dermatophytids are haematogenous infections was first demonstrated in humans by MAX JESSNER. He obtained a positive blood culture in a case of severe and extensive dermatophytid, one day after the appearance of the eruption. The recovered organism was the same as that found in the primary focus in the scalp. Soon after a similar finding was reported by AMBROSOLI. In a patient with a Microsporon audouini infection of the scalp which had been treated with X rays, ARZT and FUHS recovered this fungus from the blood three days before a generalized lichenoid dermatophytid appeared. PECK reported a positive blood culture in a case of a dyshidrotic dermatophytid of the hands.

In the presence of a severe fungous infection without a dermatophytid the injection of trichophytin will often cause an *"id" eruption*. Where dermatophytids are already present, the injection of trichophytin will not only cause a positive local reaction but an exaggeration of the existing secondary eruption. This has been demonstrated by BLOCH, SUTTER, GUTH, ARZT and FUHS and others.

The finding of fungi in *"ids"* is very rare and has only been demonstrated in the earliest lesions. As has been stated, on reaching the

sensitized skin, the fungi are quickly destroyed. The rapid disappearance of fungi in "ids" is another confirmation of the concept that dermatophytids are haematogenous infections in an allergic skin. GUTH was the first to report finding mycelia in a lichenoid dermatophytid. This was confirmed by SUTTER, ARZT and FUHS, MAX JESSNER, AMBROSOLI, MARTINOTTI and PECK.

PECK performed an interesting experiment to support the concept



757 Lichenoid dermatophytid
*(M. Jessner–New York)*

that some of the dyshidrotic eruptions of the hands are dermatophytids, secondary to a fungous infection of the feet. He produced an epidermophyton infection of the feet in a previously well, trichophytin-negative individual. The trichophytin reaction became positive in 13 days, and a slight dyshidrotic eruption appeared on the hands 24 days after the experiment was begun. Fungi could not be found in the hand lesions. After spontaneous healing of the first infection the feet

of the same patient were reinfected with the same organism. The second infection of the feet was followed in two weeks by a typical dyshidrotic eruption on the hands. The trichophytin reaction was positive at the end of the experiment.

## SYMPTOMATOLOGY

Dermatophytids may be generalized or localized and may appear in a wide variety of clinical forms. These eruptions are seen together with primary superficial fungous infections of the glabrous skin—as for example the feet, or crural areas—or with superficial or deep infections of the scalp or other hairy areas. In most instances the "ids" notably the eczematous variety on the hands, are unaccompanied by any constitutional symptoms. In some cases of generalized dermatophytids secondary to deep infections of the hairy areas, such as kerion constitutional symptoms may be observed. Under such circumstances there may be complaints of malaise, headache, fever chills, vomiting, and muscle and joint pains. Regional and general lymphadenopathy leukocytosis, enlarged spleen and swelling of the joints have been noted. Constitutional symptoms such as fever and chills may however also be observed in the erysipelas-like "ids" secondary to fungous infections of the feet. Symptoms of a systemic nature have been provoked in cases of dermatophytids following the injection of trichophytin (Bloch).

*The most commonly encountered dermatophytids are the eczematous and the lichenoid.*

A. *The eczematous "ids"* may be dyshidrotic or squamous in form and are usually found associated with a primary focus of infection on the feet or other areas of the glabrous skin. The dyshidrotic variety practically identical clinically with dyshidrosis (Tilbury Fox) or cheiropompholyx (Hutchinson), consists of deep seated vesicles appearing in crops, symmetrically distributed and usually on the sides of the fingers. They may be found also on the dorsal surfaces of the fingers the palms, particularly on the thenar eminences on the plantar surfaces of the feet and the dorsa of the toes. At times the vesicles may be so small that they will only be seen with light

coming at a proper angle. The vesicles may rupture spontaneously or dry and leave scaly or crusted eczematous areas

The squamous form of eczematous "id" may be preceded by the dyshidrotic variety or may appear as a primary form. There may be superficial scaling without signs of inflammation, or small or large erythematous areas surrounded by a collar of coarse scales. This form may be seen predominantly on the palmar surfaces of the hands and fingers. They may also be seen on the flexor surfaces of the wrists and the dorsal surfaces of the hands and fingers In some instances the picture of post-scarlatinal desquamation is simulated.

B *The lichenoid "ids"* usually are found on the trunk and not infrequently on the extremities as well. The eruption is symmetrically distributed and consists of disseminated or grouped, usually follicular rose red to dark red conical or flat topped papules The papules may be covered by fine scales or may become vesicular, then pustular and develop tiny crusts. In many instances these lesions are surmounted by horny spines. The lichenoid "ids" may resemble lichenoid tuberculid, lichenoid syphilid, pityriasis rosea, seborrheic eczema, lichen pilaris or lichen spinulosus. The course of the eruption may be short or it may occur in successive crops, persisting for weeks or even months.

Other less frequently observed dermatophytids have been encountered. The following varieties are among those reported the scarlatiniform, the erythema nodosum-like, the psoriasiform, the morbilliform, the erythema multiforme like the pityriasis rosea-like, the urticarial, the varicella like and the erysipelatous

## DIAGNOSIS

The diagnosis of dermatophytids especially the eczematous form, is not always simple It is generally agreed that at least the following criteria are necessary

1 A primary fungous infection should be present on the scalp other hairy areas or the glabrous skin

2. There should be laboratory confirmation of the presence of pathogenic fungi in the primary infection.

3 The primary focus should show evidence of inflammatory reac

tion either spontaneously developed or as a result of adventitious events like over treatment, friction, etc.

4 There should be a positive tuberculin-type reaction to the intra cutaneous test with trichophytin. *The positive reaction however is not in itself diagnostic* inasmuch as it may be due to a previous fungous infection.

5 Fungi usually should not be found in the secondary lesions.

6. Barring complicating factors such as secondary sensitization to medicaments or other contactants *the dermatophytid should subside after the primary infection has been controlled.*

In the case of the eczematous "ids" of the hands the eruption must be differentiated from contact-type eczematous dermatitis, dermatitis caused by primary irritants, toxic eruptions due to drugs or foods, cheiropompholyx, psoriasis, bacterids etc. *The diagnosis should be made only after thorough study of the case*

Histological examination does not present a distinctive picture and is usually not of help diagnostically

## THERAPY

The treatment of dermatophytids usually requires bland applications, wet compresses, such as a well-diluted aluminium acetate solution (1 20) or potassium permanganate solution (1 10 000). Simple lotions, emulsions and pastes with or without antipruritic agents are used. In some instances fractional doses of superficial X rays are helpful. Treatment by desensitization with fungous extracts has been tried. The reports of favourable results with this form of therapy have not been uniformly confirmed.

For the cure of the dermatophytids it is necessary to eradicate the primary fungous focus. Treatment for this will depend on the status of this infection and should vary from the above mentioned remedies in the acute stage to the use of efficient but non-irritating antifungal agents in the less acute and chronic conditions.

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CHAPTER 61

# EPIDERMOPHYTOSIS

## (Athlete's foot)

FELIX SAGHER

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### DEFINITION

Tinea of the feet is an inflammatory process occurring mainly between the toes but which may involve other parts of the foot. The causative agents are various fungi but some bacterial infections may give rise to a similar picture, and for this reason microscopic or cultural proof of the presence of fungi should be established.

Synonyms are *Ringworm of the Hands and Feet, Athlete's Foot, Hongkong Foot, Singapore Foot, Dhobie Itch, Tinea Pedis, Dermatophytosis Pedis, Epidermophytia Interdigitalis Pedis, Dermatomycosis Epidermophytica of the Feet, L'épidermophytie des espaces interdigitaux des pieds, Foot tetter, Mango Toe.*

### HISTORY

According to ORMSBY and MONTGOMERY this disease was first described by TILBURY FOX in 1870 and the first systematic study was made by DJELALEDDIN MOUKHTAR in 1892.

### EPIDEMIOLOGY

Athlete's foot is by no means a tropical disease, but it seems to be more frequent in warm and hot climates where it is of great import

ance owing to possible coccal complications Here also the eruption is usually more active and more frequently involves the groins, axillary region and hands It is the most common of all mycotic infections and is one of the greatest causes of wartime disability in warm climates That military conditions favour the spread of the infection, especially in tropical training camps has been pointed out in a number of publications (EPSTEIN FASAL, MASTER, DUEMLING etc) DELANEY



758 Athlete foot also called Hongkong foot, Singapore foot Dhobie itch, et Intertriginous type

found fungi in 80 per cent. of soldiers in the Southern Pacific during World War II

Predisposing factors are moisture, heat, maceration, friction and immunologic susceptibility (SULZBERGER)

It is also a cause of industrial disability notably in coal mining The name *dhobie itch* (washerman s itch) was given because the infection spreads by laundry but in most descriptions this term is also used for tinea cruris PECK and SCHWARTZ studied dermatophytosis of the feet

as an occupational health problem. Of 2,123 industrial workers, from various plants, 27.89 per cent. harboured fungi and 33.63 per cent. had doubtful infection. It is assumed that the virulence of the fungi is higher in highly industrialized countries. In countries without marked industrial progress the incidence of ringworm of the feet has remained at a low level. In educational establishments encouraging athletic games athlete's foot is more often seen (DUNCAN, WALLACE and MOORMAN).

Familial exposure seems to be of no importance in the spread of infection, a point established by SULZBERGER, BAER and HECHT through a questionnaire sent to 120 dermatologists in the United States. WILLIAMS, in 2,400 observations, found athlete's foot more common in men in the proportion of 1 to 1.3. In men the feet are more affected than the hands; in women the reverse is the case.

### AETIOLOGY

A large variety of fungi are capable of causing ringworm of the feet and hands. Many of those described are simply variants in several large groups which are mostly responsible for this disease. The fungi most commonly found affecting the feet and hands are *T. mentagrophytes* (synonyms *T. gypseum*, *T. interdigitale*, *T. asteroides* etc.), *T. purpureum Bang* (synonyms *E. rubrum*, *T. plurizoniforme*), *E. floccosum* (synonym *E. inguinale*), and *Candida albicans*. A number of so-called non-pathogenic fungi are often found in these lesions but there is no certain proof that they are not sometimes capable of causing disease. MUSTER and PAILLARD believed that *Scopulariopsis* was responsible in their cases, and others incriminate *Candida tropicalis*, fungi of the *Aspergillus* and *Penicillium* groups, etc.

Culture of fungi from the feet and their identification succeeds only in about 50 per cent. of cases in spite of positive microscopical findings. Further, only half of the "clinical cases" are positive microscopically and in processes affecting the hands the figure drops to 5.6 per cent. (STRICKLER, EPSTEIN). These facts are confirmed by most mycologists. A possible explanation is that this is due to methods and interpretation in the culturing of fungi. It may be that some of the microscopically positive findings represent fungi later assumed to be non-pathogenic when found in the culture, or that the disease is not due to fungi at all

in spite of microscopically positive findings Only unimportant differences were found between the types and percentages of pathogenic fungi cultured in the laboratory by LEWIS and HOPPER in New York, and in the Dermatological Department of the Hadassah University Hospital in Jerusalem.



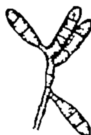
759 Athlete s foot. (Squamous type)
*(Simons– Amsterdam)*

RESULTS OF CULTURES OF MATERIAL FROM FEET

| | No of Cases | | Per cent. of Total Cases | |
|---|---|---|---|---|
| | New York | Jerusalem | New York | Jerusalem |
| *T gypseum* (all varieties) | 80 | 36 | 37.2 | 18 7 |
| *T purpureum* | 24 | 3 | 11 1 | 1 6 |
| *E floccosum* | 1 | 1 | 0.5 | 0 5 |
| *M albicans* | 1 | 3 | 0.5 | 1 6 |
| Yeast like fungi | | 32 | | 16.6 |
| Unidentified | | 3 | | 1 6 |
| No growth | 109 | 115 | 50 7 | 59 4 |
| TOTAL | 215 | 193 | 100 0 | 100 0 |

MONTGOMERY and CASPER summarized 1,557 cultures from affected feet in 65 4 per cent. *T mentagrophytes* was found, in 17.5 per cent *T purpureum* in 13.5 per cent, *Monilia albicans* and in 2.8 per cent.





760. 761

Epidermophyton floccosum (Harz) or E. cruris (Castellani), E. inguinale (Sabouraud and E. clypeiforme (MacCarthy). Note cl bshaped macroconidia in bouquet formation. Chlamydospores may be present under the surface of the colony The colony shows radial furrows and is greenish in colour It grows slowly and pleomorphism readily occurs (see Chapter 55) Although epidermophytosis as a synonym of athlete s foot has been called after the epidermophyton, a great number of cases are due to other fungi

(*Simons–Amsterdam*)

*E floccosum* the remainder were unidentified. The main difference in the findings from the hands was the growth of *Monilia albicans* in 55 1 per cent. Similar figures have been found by most authors, with some differences due to local strains.

## PATHOGENESIS

The importance of the surface film acidity in the sterilising power of the skin has been repeatedly stressed The usual acidity of pH 4 to 5 is remarkably reduced in skin folds and interdigital spaces to a pH of 6.5 to 8. This change in pH is partly caused by the relative lack of eva poration in these areas. Observations among Belgian Congo Negroes

serving in Southern Palestine during World War II revealed a high incidence of athlete's foot. According to the army physician the disease was practically unknown before the soldiers were enlisted and wore boots for the first time. HERRMANN MARCHIONINI and later PECK and ROSENFELD attempted to change the acidity in these folds as a therapeutic measure.

## FURTHER AETIOLOGIC CONSIDERATIONS

The main aetiologic factors are expressed by the words "soil, warmth,



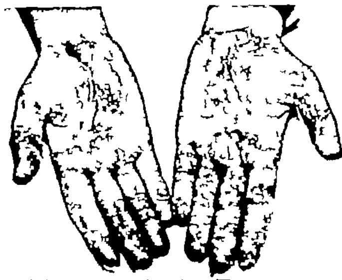
62 Athlete's foot vesicular type

moisture, sweating" Athlete's foot is very rarely seen in childhood and mostly starts after puberty Ringworm of the groins sometimes precedes the outbreak or is present simultaneously

Sources of infection are generally thought to be showerbaths and dressing rooms. PECK who examined the floors of shower rooms, did *not confirm this widespread opinion.*

The fungi often lie dormant under or around the nails in subungual keratoses or in callouses without causing harm to the patient, and

often these signs may pass unnoticed for years. Heat, moisture and general deterioration in the patients health may cause the development of active symptoms In spite of the fact that the clinical signs appear mainly in summer there are some patients who continue to suffer throughout the whole year In the Middle East a re-activation of the condition is often seen after so-called "Chamsin Days" on which a dry hot wind from the desert blows over the country



763. Epidermophytosis of the palms of the hands. Squamous type. Primary infection of the feet

## SYMPTOMATOLOGY

Various clinical types are generally recognized. These may be coexistent or follow upon each other Inguinal lesions may be present or precede the lesions of the feet.

1 *The vesiculo-bullous type* is characterised by deeply seated, small, tense, slightly inflammatory vesicles, similar to vesicular eczema or dyshidrosis. The vesicles are located on the plantar and palmar surfaces of the toes and fingers, rarely on the dorsal surfaces, and also in the interdigital spaces and on the soles. The vesicles are grouped and their appearance is often accompanied by marked itching Their con-

tents are clear but the fluid may become infected or may be reabsorbed leaving a brownish macule which scales off revealing a moist red surface. If there is no desquamation a brownish hyperkeratotic plaque may be produced.

2. In *the squamous-hyperkeratotic type* there are no vesicles Desquamation may be found over the entire sole and is characterised by sharply outlined scaling borders. Localised hyperkeratosis or a keratoma plantare-like picture can appear in which *T purpureum* is often found. Generally small irregular patches are formed with sharply marginated borders.

3 *The intertriginous type* is the most common and is found in a very high percentage of the adult population especially in warm countries. The signs are often unnoticed until propagation of the disease occurs. Very commonly a fissure underneath the fifth toe is present or an interdigital fissure between the 4th and 5th or 3rd and 4th toes which remains unnoticed until subjective symptoms appear Further a whitish macerated keratotic mass between the toes may be seen, which when removed leaves an erythematous plaque. The location of the lesion is according to frequency the fourth interspace of the foot the plantar area of the arch, and over the fifth metatarsus. Hyperidrosis of the hands and feet is frequently associated with athlete's foot. The dyshidrotic type occurs mostly in winter the intertrigonous in summer. Subjective symptoms may be absent, or there may be moderate or severe itching or burning and pain in the acute eruptions with eroded surfaces

Montgomery and Casper believe that certain clinical forms are typical for certain fungi *T mentagrophytes* being characterised by vesicle formation, *T purpureum* by desquamation and keratosis of the soles, and *E floccosum* by vesicles and large scales *Monilia albicans* produces interdigital erosions which progress only in the vicinity of the interdigital spaces.

## EPIDERMOPHYTID

The primary infection of the feet can produce eczematous eruptions on the hands This may be caused by allergic reactions as a result of repeated, usually hematogenous transfer of small numbers of fungi or

See Chapters 60 92 and 93

their products to the hands These "ids" are fungus-free. The clinical appearance of the ids may be vesicular, bullous or scaly and is often dyshidrosiform. The generalized form of "id" is uncommon. The diagnosis of these ids should be based, according to SULZBERGER and BAER, on the following criteria a primary fungous focus must be present the eruption of the hands should have followed an irritation of this focus the location on the hands should be symmetric, especially on thenar and hypothenar eminences palms and sides of the fingers the affection of the hands should subside after a reasonable period following control of the primary focus and it should be possible to



764 Epidermophytosis.

*(Siemens Amsterdam)*



765 Shoe-lining eczema, often taken for epidermophytosis, particularly when secondarily infected with fungi.
*(Siemens—Amsterdam)*

elicit a positive intradermal reaction of the tuberculin type.

Many authors believe that disseminated lesions on the hands may be caused by external transplantation of the fungus. PECK produced a pompholyx of the hands following experimental inoculation of the feet with an *Epidermophyton* but no fungi could be demonstrated in the lesions of the hands.

## COMPLICATIONS

A not rare complication of athlete's foot is a recurrent, erysipelas-like dermatophytid on the lower extremities. This complication was thoroughly discussed by SULZBERGER, TRAUB and TOLMACH, and cases were studied by WAISMAN, NAIDE, THOMPSON, HOLMAN and others. The onset of this complication is often preceded by an exacerbation of the primary focus. The erysipelas like eruption may be accompanied by general symptoms as in true erysipelas but may also appear without any general disturbances. A negative trichophytin reaction was observed in these cases after 48 hours but a positive immediate wheal response was obtained. This latter reaction is stronger at the fixed site of the erysipelas-like eruption than at other skin sites. It is assumed that this inflammatory erysipelas like dermatophytid is caused by products of the fungus. The eruption is not influenced by sulphonamides or penicillin. These statements are no contradiction of the fact that true erysipelas can occur in the lower extremities, where athlete's foot may furnish a portal of entry for the streptococci.

A similar conception as for the erysipelas like complications has been thought to be true for some cases of thrombangiitis obliterans and HOLMAN reported good results in treating two cases with trichophytin.

Secondary infection with pyogenic organisms may lead to cellulitis, lymphangitis and lymphadenitis. CLEVELAND WHITE found the same species of fungi in an inguinal adenopathy as in the original interdigital lesion. The activation of a fungous infection of the foot owing to the administration of penicillin is not rare.

## HISTOLOGY

Changes similar to those seen in eczematous dermatitis are found. There is according to MONTGOMERY intracellular oedema and spongiosis with intra-epidermal vesicles. The vesicle contains polymorphonuclear leukocytes fibrin and epithelial cells. Fungi can be found lying parallel to the surface in the upper part of the stratum corneum. A slight non-specific infiltration is found in the papillary and subpapillary layers, especially in the vicinity of the vesicles

## DIAGNOSIS

Many dermatoses simulate the clinical picture of athlete's foot, together with its id eruptions, and therefore not all inflammatory processes of the feet should be diagnosed as athlete's foot. Contact dermatitis due to leather, coccal infection, psoriasis, disturbances of the sweat glands, lichen simplex chronicus, persistent erythema of the palms and soles, pustular bacterid, ainhum and syphilis may be differentiated only by the positive finding of the fungus. Among 100



66. Secondary syphilis of the soles of the feet which might erroneously be regarded a form of epidermophytosis.

(*Zoon, Utrecht*)

affections on the feet, SICOLI in Paris found 42 per cent. due to fungi, 34 per cent. due to dermatitis medicamentosa produced by phenol salol, iodoform etc., and 24 per cent. were sterile. HOPKINS and coworkers found 30 per cent. of cases with clinical athlete's foot to be negative for fungi. Eruptions on the hands are too readily diagnosed as ids and should be differentiated from cheiropompholyx, which usually starts on the thumb, on the dorsal rather than flexor surface, and is more definitely bilaterally located than is fungous infection.

Occupational dermatitis, contact dermatitis, eczema due to food, dermatitis repens, erythema multiforme, pellagra, infectious eczema

toid dermatitis due to scabies, drug eruptions and lichen planus (especially in subtropical countries) may often be mistaken for an id reaction of athlete's foot. Because of such possibilities the microscopic finding of the parasite is the essential method for the diagnosis of ringworm. In the absence of the fungus, as in id reactions all the clinical features described above should be taken into consideration.

### TRICHOPHYTIN TEST

PECK performed trichophytin tests in 776 workers in industrial plants and 42.53 per cent. reacted positively More men were positive than women. The test was more often positive in workers with active signs of ringworm on the feet or hands than in those without clinical signs. However since the test remains positive for many years after cure of the disease it is of limited diagnostic value, and only confirms that a fungous disease is or was present.

### PROGNOSIS

The disease tends to recur but its prognosis depends largely on the type of fungus invading the skin. Further it is important to note that the nails are often invaded by fungi and may act as a focus from which the skin can be reinfected. For this reason the nails should be examined clinically and microscopically and when infected should be treated adequately Scrapings of 2,000 nails from the hands and feet of 118 patients with various dermatophytoses were examined microscopically and mycelia were found in the nails of 61 patients (DOSTROVSKY RAUBITSCHEK and SAGHER) The clinical picture of the nails often suggests the type of the invading fungus for instance foci of yellowish stained leukonychia is caused by *T mentagrophytes* transverse furrows on the lateral parts of the nails are characteristic of *Monilia albicans* thick subungual keratotic masses and a yellow brown colour of most of the toe nails is often found in *T purpureum* infections Histologic examination of these nails revealed different centres of localisation, different fungal arrangements, and nails damaged in different ways by various fungi *T purpureum* for instance, was found chiefly in the deepest layers of the nail plate and never in the superficial layers (SAGHER) No external medication will reach these fungi and these nails furnish in this way a permanent source of reinfection.

Experience teaches that the prognosis is best in infections which are due to *Monilia albicans* and *T. mentagrophytes* less good in *E. floccosum* and worst in *T. purpureum*

#### THERAPY

Since no specific remedies against fungi exist, treatment has to be based on general dermatologic principles. SULZBERGER repeatedly stressed the fact that treatment cannot be based on laboratory estimations of the fungicidal or fungistatic activity of a medicament. Strong remedies and overtreatment may cause irritation and additional trouble. He believes it improbable that even antifungal antibiotics will bring a revolutionary change. It cannot be expected that such antibiotics will kill all superficial fungi just as penicillin does not permanently eliminate all staphylococci from the skin.

Not all of the many methods of treatment of athlete's foot can be mentioned, and only the main drugs and the points of logical treatment will be stressed. That the result of treatment is not always satisfactory may be because of climatic conditions, predisposing factors such as hyperidrosis, the difficulty of radical changes in the footwear, and the species of fungus present. The treatment should consist of first alleviating the symptoms and complications, followed by mechanical removal of fungous masses in the macerated skin, and finally the application of medicaments in order to attack the fungus. There is no attempt at direct extermination of the fungus but rather at a change of the parasite-host equilibrium in favour of the latter

The acute stage is best treated by wet dressings of Burow's solution, potassium permanganate of 1 in 8 000 dilution, solution of sodium thiosulphate of 1 in 200 silver nitrate of 1 to 1 000 etc. Opening of vesicles and pustules should be performed during a bath with one of these solutions.

A large number of preparations have been recommended for the subacute and chronic types. Whitfield's ointment containing 12 per cent benzoic acid and 6 per cent. salicylic acid in petrolatum Dreuw's ointment containing 10 per cent. salicylic acid, 20 per cent. chrysarobin in green soap and an ointment base, as well as Wilkinson's formula, is widely used among dermatologists. Chlorophyll ointment has also been recommended. Further useful chemical agents are

iodine 3 to 10 per cent., carbol fuchsin 1 per cent. or in Castellani's mixture, brilliant green, gentian violet, acriflavin, methylene blue, malachite green. Balsam of Peru, ammoniated mercury β-naphthol, chrysarobin, resorcinol, tar boric acid, borax and formaldehyde are other favoured preparations. Copper sulphate has been advocated using ionophoresis A phenol camphor preparation consisting of equal quantities of pure phenol and pure camphor triturated until liquefied has been used. Excellent control studies showed the value of phenylmercuric salts (GOLDMAN and co-workers) calomel ointment, cresatin which is metacresylacetate (WEIDMAN and GLASS) ethyl para oxybenzoate (HOLM) etc.

Hyperkeratotic lesions should be treated with salicylic acid ointment in strengths up to 20 per cent. iodine solution or Arning's tincture also carbon dioxide snow and ethyl chloride spray have been recommended A great hope was the introduction of the fatty acids such as undecylenic acid, propionic acid and caprylic acid, but so far these preparations have disappointed somewhat in treatment although they have kept their place as prophylactic agents

It should be mentioned in general that the use of ointments compares less favourably in hot climates to the use of dyes, solutions and tinctures because of chemical changes which are often followed by irritation of the skin.

## PROPHYLAXIS

HOPKINS and co-workers have found that the same causal organisms could be cultured in most recurrent attacks of fungous eruptions of the feet. It may be concluded from this that most attacks of athlete's foot are recurrences and not new infections. For this reason prevention should aim mainly at overcoming the infection in the non-active stage of the disease, besides the usual hygienic methods In general the following points are of importance in the prevention of athlete's foot

1 Continuation of local therapy during the inactive stage of the disease Dusting powders containing undecylenic acid camphor precipitated sulphur zinc sulphate boric acid, or tannic acid may be of great value in this inactive stage. These powders can be used alternately with weak iodine chrysarobin solutions or aniline dyes.

2. The nails as potential foci. Their treatment may be very difficult, and often even evulsion fails to destroy this focus.

3. Avoidance of wooden duck-boards in the bathroom or shower room and avoidance of contaminated public baths and sea-shores. The disinfection of the bathroom can be done with a solution of sodium thiosulphate 1 to 200.

4. Care of shoes, stockings and socks. The type of footwear in use may be a predisposing factor because the sweat cannot evaporate properly. For this reason infections are seen mostly in males rather than in females who wear open-toed and more ventilated types of shoes. NICKERSON and associates carried out a controlled study of this question. One thousand two hundred soldiers who received sandals during the summer months showed a considerably lower incidence of athlete's foot in comparison with a control group. Washing and thorough drying of the interdigital spaces followed by the use of dusting powders applied to the skin or into the socks is of great value. Moderate exposure of the feet to sunlight and avoidance of heavy sweat-soaked and infected shoes is recommended. The shoes can be disinfected during the treatment, although their role in re-infection is not definitely established. They are best treated with mercury solutions, formaldehyde or with insoles containing antifungous agents. Sometimes, however, these may cause a contact-dermatitis (see Fig. 765).


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CHAPTER 62

# ERYTHRASMA

A. GONZALEZ OCHOA

*Mexico D.F.*

## DEFINITION

Erythrasma is an epidermomycosis characterized by its intertriginous localization, particularly inguinal, with reddish to brownish superficial patches caused by an Actinomycete, *Nocardia minutissima* (BUCHARDT) VERDUN 1912.

## EPIDEMIOLOGY

The infection occurs throughout the world, but is more frequently met with in tropical countries. It predominates in the adult male; the female is rarely affected, and it is not seen in children. Its contagiousness is low which is concluded from the observation that in marriage if one spouse suffers from erythrasma the other may remain uninfected.

## SYMPTOMATOLOGY

The onset is generally unnoticed, but in rare cases in which it has been observed it appears as punctiform or medallion maculations, which grow slowly until they form patches from 5 to 20 cm in diameter. The colour varies in relation to age and activity of the lesion. In younger ones it exhibits a vivid redness, in older or mild lesions the discoloration is brownish to yellowish. The neat and well-limited borders present a sharp contrast with the surrounding tegument. The contour of the patches is irregular or polycyclic when it is due to the confluency of

some lesions, and sometimes small plaques are seen surrounding the central lesion The patches are not raised above the level of the skin, but sometimes the border shows slight elevation, although no vesiculation or papulation is observed. The surface is frequently slightly squamous, while others are smooth and moist making it difficult in these cases to obtain scales by scraping Frequently the epidermis is neatly wrinkled and dry In general it is a dermatosis with a mild inflammatory reaction subjective symptoms are absent, or only a slight pruritus is present.

The most frequent localization is inguino-crural, predominating on that side in contact with the scrotum, although the scrotum itself is not generally affected. In some cases spreading of the lesions to the inferior region of the abdomen and intergluteal fold is seen. In order of frequency after the above localizations, the axillary comes next, the lesion being of the same characteristics as that of the inguino-crural. It can also be found in any other part of the body where cutaneous surfaces remain in contact, as the interdigital spaces of the feet and the inframammary fold. In very rare instances cases have been recorded in which the lesions disseminate profusely and invade the free cutaneous surfaces, as in the neck, chest and back.

Except in the rare localizations of this disease, or when there are complications such as cocci infections, dermatophytosis, or a super imposed medicamentous dermatitis, the erythrasma is of very easy clinical diagnosis. In the differential diagnosis tinea cruris, moniliasis, hyperhidrosis and intertrigo dermatitis venenata caused by cosmetic applications preferably in its axillary localization, pyoderma, eczema, lichen planus and some rare forms of parapsoriasis should be considered. The finding of *N minutissima* in the scales will confirm the diagnosis.

The prognosis is benign, but the evolution is one of great chronicity in some cases, in which even under a well conducted treatment the infection persists for months recurrences are frequently observed.

## DIRECT EXAMINATION

Owing to the thinness of the parasite it is difficult to see it in the usual media for clarifying scales, such as KOH and the chlorallactophenol d Amann It is necessary to stain the scales by some of the current

methods The one suggested by MUSKATBLIT gives good results it consists in pasting the scales by means of raw egg white, and, when dried, in fixing and defatting in Carnoy's fluid during five minutes. After the slide is dried it is stained with polychrome methylene blue for five minutes, washed in water for two minutes decolourized with 1 per ct. aqueous solution of acetic acid for one to two minutes and after five minutes in xylol, the specimen is mounted in Canada balsam or clarite. In those scales so stained the micro-organism is seen abundantly as short, flexible very thin filaments, 0 6 to 0 8 μ in width, rarely they reach 1 μ their length is 5 to 20 μ and most of them are



767 Erythrasma of the armpit Note separate lesion on the chest

seen formed by a chain of coccoid and bacillary elements due to the fragmentation of the filament also these coccoid and bacillary elements are found spread out or in clumps among the filaments

The N *minutissima* is an Actinomycete, very difficult to cultivate and probably it has not yet been cultivated since authors who have reported success have had discordant results

**TEST**

The limitation of the parasite to the stratum corneum and the slight

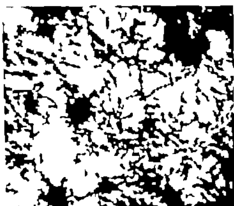
ness of the inflammatory reaction make haematological and immunological reactions nugatory

### DIAGNOSIS

The presumptive diagnosis is obtained from the described clinical picture but its verification is attained only by the observation of the parasite in the scales after they are stained. The existence of very thin branched filaments, with a diameter similar to that of a bacillus, formed by juxtaposition of coccoid and bacillary elements and by their clumps is very characteristic of *N minutissima*

### THERAPY

In the simple forms the treatment will consist in the use of a kerato-



68. Nocardia minutissima in scales. Filaments and their bacillary and coccoid fragments.

lytic associated with a fungicide substance. In the complicated cases the treatment of the complication will be attended to first. The keratolytic of choice is salicylic acid at 3 per cent. or thereabouts, and as fungicides, anthrarobin at a concentration of 3 to 10 per cent. in benzoin tincture is the first choice chrysarobin is very active, but it should be used with caution as it produces dermatitis and only in the dry forms, and at concentrations not higher than 3 per cent. iodide alcohol of 1 per cent is very effective. It is necessary to

continue the treatment for several weeks after the apparent cure, otherwise there may be a recurrence the clothes in direct contact with the affected skin should be disinfected by boiling

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CHAPTER 63

# OTOMYCOSIS

## (Hot weather ear)

A. W. THÖNE

Leyden

### DEFINITION

The term otomycosis implies any fungous disease of the ear the fungus being either the actual cause or merely a secondary invader or contaminant in otitis externa with a different aetiology. Synonyms are, *Singapore ear, Hongkong ear, fungus ear, hot weather ear*.

### HISTORY

MAYER was the first to draw attention to infection of the external ear by fungi (1844). WREDEN (1868) wrote a monography on myringomycosis (infection of the eardrum due to fungi).

### AETIOLOGY

The fungi said to cause otomycosis are numerous. WOLF collected 53 species from the literature, of which *Aspergillus* (90 per cent.) *Penicillium*, *Mucoraceae* and *Candida* are the most important. The chief problem in otomycosis is, what is the part played by the fungus in the morbid process.

There are three possibilities, *i.e.*,

(a) the fungus is the true initially invading parasite, alone responsible for the inflammation. This would be the case with the reported infections of the ear by *Candida albicans* and the few reports of infections by *Malassezia furfur* causing pityriasis versicolor of the external auditory canal (OERTEL), *Achorion* (WHALEN) and *Actinomyces*

without any symptom. In most cases, however the following symptoms are encountered (CONLEY) Mild to severe itching in almost every case a sense of fullness due to mechanical obstruction loss of hearing possibly associated with tinnitus aching or a dull pain, and a moderate discharge. HATCH and ROW (quoted by CONLEY) distinguish two types a weeping type with exudation and a dry squamous type. The desquamation and other debris may form such a plug that DAMOND (quoted by BENJAMINS) called the condition cholestéatome de l oreille externe

The filling of the ear is described by most authors as having the



771 North American blastomycosis of the ear
*(Aars-Carayon)*

appearance of blotting paper or of a pulpy mass consisting of epithelial debris, cerumen and mycelium. In very evident cases the mycelium can be recognized as such. On this pulpy mass the conidiophores may sometimes be seen as little specks in different colours according to the strain of fungus (*Asp niger Asp glaucus* etc.) In some cases the membranes are very adhesive and difficult to remove. The inflammation is localized in the bony part of the auditory canal, and may spread to the eardrum (myringomycosis) In some instances the fungus

was found to have invaded the eardrum (OERTEL) even perforation may occur (PLAUT TREXTER, SALZBERGER quoted by DART). When the eardrum has been perforated the fungus may invade the middle ear anthrum and mastoid cells Furunculosis is a frequent complication and perichondritis due to secondary pyogenic invasion has also been described. Unless treated the condition tends to become chronic.

## DIAGNOSIS

Seborrhoeic eczema has been erroneously diagnosed as otomycosis and should be excluded by inspection of the other predilection places of the former affection. The possibility of pyogenic infection of the external ear, either as such or secondary to pediculosis capitis, should



772. Otomycosis spread to the eardrum, when called myringomycosis. Aspergillosis of the eardrum.

*(Passow–Trommelfell bilder Publ. Fischer 1912)*

be considered. Contact dermatitis of the external ear must be differentiated.

Without at least microscopic examination, or better still, a culture, the diagnosis of otomycosis is not justified.

## THERAPY

The chief prophylactic *principle is to keep the ear dry.* In hot and moist climates the ears should be plugged with cotton wool during bathing or swimming.

Before starting treatment a thorough inspection should be made whether the eardrum is perforated, in this case there is a chance of

pathogenic organisms being carried deeper into the ear. According to KING GILL (quoted by DART) the four principles of treatment are,

(1) to cleanse the external ear mechanically as carefully as possible, avoiding any trauma or maceration of the skin.
(2) to reduce local inflammation and allay pain.
(3) to limit sporulation.
(4) to leave the parts in such a condition as to prevent recurrence.

As the best fungicide of his choice for otomycosis KING GILL mentions metacresylacetate 1/1000 (proprietary name cresatin). Thymol 1–2 per cent in alcoholic solution has also a good reputation. The commonly used 2 per cent. alcoholic solution of salicylic acid has only slight fungicidal properties, but may be useful as a keratolitic. WHALEN describes the following technique. The canal is first cleared by irrigation and dried by hot air. It is then packed with absorbent cotton wool soaked in cresatin. The patient is ordered to remove the packing the following morning. After the packing is removed an attendant injects 6 drops of a 1 per cent. thymol solution in 70 per cent. alcohol into the canal. The thymol treatment is repeated twice daily for five days; it usually produces a burning sensation. A thymol iodide powder is then prescribed to be blown into the ear for another five days.

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CHAPTER 64

# MYCOTIC INFECTION OF THE EYE

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Leyden

Reports of mycotic infection of the eye are rare only keratomycosis is a special entity with its own chapter in ophthalmological books

## KERATOMYCOSIS

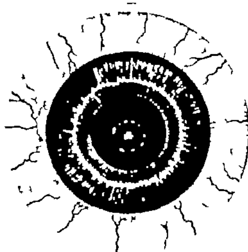
In keratomycosis there is invariably a history of a lesion of the cornea by a foreign body such as mud, cow-dung or some vegetable object without trauma fungous infection does not seem to occur (SCHIECK)

The causative organism in most instances is *Aspergillus fumigatus* but *Actinomyces* *Mucor mucedo* *Glenospora graphii* and *Cephalosporium* are also mentioned (DUKE ELDER). The disease is a slow chronic process gradually following the lesion, a greyish superficial necrosis forms with a dull, dry surface, surrounded by a sharp yellow line of demarcation. Microscopically the mycelium is seen as a network in the superficial layers of the cornea. The line of demarcation consists of leucocytes. There may be serious pain hypopyon and iritis are frequent complications. After sequestration the lesion tends to heal. Perforation of the cornea is rare but if it occurs the fungus may invade the vitreous, uveal tract and the retina. Even panophthalmitis is reported. If the lesion is localized near the limbus the sequestrum forms more rapidly and vascularization may occur The species *Mucor mucedo* forms a loosely adherent pseudo-membrane Treatment consists of ablation of the infected superficial part of the cornea

followed by cauterization. As in spontaneous sequestration, restitution after this procedure is rapid (DUKE ELDER)

#### EYELIDS

The skin of the eyelids and the cilia may be infected by *Achorion schoenleini* and by *Trichophyton* and *Microsporon* species *Favus* seems to be located only on the upper eyelid. *Actinomyces* yeast-like organisms and *Blastomyces* (Gilchrist) may affect the eyelids especially the latter organism has a prevalence for the eyelids (see frontispiece, *Manual of*



773 Actinomycotic ulcer of the cornea three weeks after a slight injury (*Arnold Loewenstein*)

*Mycology* CONANT *et al*) Also Sporotrichosis with a swollen lymph vessel leading to the preauricular and submandibular lymph glands has been observed (SCHREIBER)

#### LACHRYMAL APPARATUS

DONAHUE in a recent article describes a case of infection of the lachrymal sac, duct and canaliculi by *Aspergillus fumigatus* A young girl had an epiphora and a black, discoid, slightly elevated area around the lower punctum lachrymale of several weeks standing There was

complete occlusion of the lower punctum. After a tiny incision a sticky fluid was expressed and the discoloration disappeared. The patient was completely relieved of epiphora and other symptoms Culture yielded *Aspergillus fumigatus* The fungus in this case merely produced occlusion, and after mechanical clearance no further trouble was experienced. According to the author concretion of the canaliculi by *Leptothrix* and *Actinomyces* is not so rare in these cases the whole apparatus may also be involved. *Sporotrichum* and *Rhinosporidium* are also reported to have invaded the lachrymal sac.



774 Sporotrichosis of the eye secondary to a gummatous form on the face (*González Ochoa—Mexico*)

## CONJUNCTIVA

Fungous infection of the conjunctiva is rare, although FAZAKAS (quoted by DUKE ELDER) found fungi present in 24 per cent. of healthy eyes. *Leptothrix oculorum* (BRUMPT) is the cause of a unilateral subacute nodular conjunctivitis with lymphadenitis showing yellow or grey areas under the conjunctival epithelium. The incubation period is 3–7 days. Ulceration does not occur the cornea is not affected but infiltration may be considerable. Children and young adults are mostly affected. Primary *Actinomycosis* (usually called *Streptotrichosis* by ophthalmologists) is a chronic recalcitrant nodular lesion sometimes combined with canaliculitis. Most frequently the

conjunctiva bulbi is affected, showing little yellow nodules. Also catarrhal conjunctivitis of the angular type may be encountered. Treatment consists of excision and washing with potassium iodide. Sporotrichosis conjunctivae forms small, yellow soft, sometimes ulcerating nodules, regional lymph nodes being involved. Rhinosporidosis was seen to be limited to the eye in 14 per cent. of cases reported by KARUNARATNE (cited by CONANT *et al.*). In the early stages there are small, yellow to pink, granular nodules which are freely movable. Later these nodules may grow into polypoid, speckled, easily bleeding tumours. Treatment consists of surgical measures and a 2 per cent. emetine eye lotion (WRIGHT cited by TOULANT). *Candida albicans* and even *Achorion* and *Trichophyton* were reported to cause conjunctivitis either with or without involvement of the adjacent skin (DEUCHLER cited by DUKE ELDER).
MUENDE mentions a case of conjunctivitis as a trichophytid manifestation after X ray epilation for Trichophytosis capitis in a boy.

## UVEAL TRACT ETC.

Mycotic infection of the uveal tract, vitreous and retina are still more rare. Aspergillosis and candidiasis are mentioned after perforation of the cornea. A case of actinomycosis of the retina was reported by MUELLER (cited by DUKE ELDER).
LEVITT described a case of coccidioidomycosis of the lung complicated by vitreous opacities and a retinitis of the proliferative type. These eye manifestations cleared at the same time as the lungs and were interpreted as being caused by *Coccidioides immitis*.

## ORBITA

Actinomycosis of the orbita may occur as a result of an infection of a tooth in the upper jaw.

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# MONILIASIS

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In the history of dermatological research there have been hardly any micro-organisms which caused such a profound confusion as the yeast like organisms commonly called *Monilia*

## MYCOLOGY

*Candida albicans Berkhout* 1923 —The genus Candida contains numerous species (DIDDENS and LODDER) of which only one, Candida (Monilia) albicans is of particular interest for dermatologists The genus Candida develops a pseudomycelium (also to a smaller extent a true mycelium) with blastospores in arrangements which may be typical for some species chlamydospores may also be present. BENHAM found that strains of C. albicans vary both in morphology and virulence. The morphological variation is toward a more membranous type of growth and increased mycelial development.

*These yeast like organisms are known as "monilias" to the American workers and "mycotorula" or "candida" to the Europeans* In the further discussion the facultative parasite from human sources will be designated as *Candida albicans* and the clinical forms of the affliction as *moniliasis*

Cultures of C. albicans are easy to obtain at room temperature on beer wort agar on Sabouraud's glucose or maltose agar The giant colonies show a smooth centre with filamentous edges their colour is white or creamy In older colonies the surface is interrupted by tiny craters areas where the gas formed in the medium escapes The

colony grows into the medium causing the appearance of the so-called "inverted fir tree" Due to gas formation the agar media are disrupted in older cultures Mycelia with terminal chlamydospores and spore clusters at regular intervals are present. Reproduction is by budding Budding cells are slightly oval and fairly regular in size.

Space does not permit going deeper into the taxonomy morphology and biology of this organism. The student may consult the excellent monographs of LODDER, FISHER and ARNOLD, and MACKINNON

## OCCURRENCE OF YEAST-LIKE ORGANISMS ON THE SURFACE OF NORMAL SKIN AND NORMAL MUCOUS MEMBRANES

*Yeast-like organisms of the mouth* 10 per cent of one thousand normal throats were found to contain yeast like organisms (TAMURA *et al*). In children up to six years of age, 38.5 to 54 per cent. were found to contain the thrush fungus (EPSTEIN) 19 per cent. of normal commissures of the mouth contained yeast-like fungi (FRANK).

*Yeast-like organisms of the gastrointestinal tract* The percentage of normal individuals showing yeast-like fungi in the faeces varies widely according to different workers: ANDERSON found 47 per cent. positive for fungi DOLD found 7.5 per cent. FLEISCHER and WACHOWIAK reported 38 per cent. WACHOWIAK *et al* found 6 per cent. ASHFORD observed 44 per cent. BENHAM found 80 per cent of all types of fungi, 18 per cent. being C. albicans.

*Yeast-like organisms of the vagina* Many workers have found yeast-like organisms in the vagina under various conditions – pruritus vulvae associated with pregnancy diabetes, vaginal thrush, chronic vaginitis, leukorrhoea, and also asymptomatically Numerous different organisms have been cultured, but Candida albicans has been mentioned most frequently DODERLEIN found 36 per cent. of normal vaginas positive for C. albicans. PLASS *et al* found 24 per cent. to be positive, of which 17 per cent. were in normal pregnant women. JOHNSON and MAYNE found yeast-like organisms in 37 per cent of 667 pregnant women on routine cultures in a prenatal clinic. These were identified as C. albicans in 42 per cent., C. stellatoidea in 37 per cent. of the cases Trichomonal and yeast-like infections were found to coexist in 9 8 per cent of 654 of these women. Of 98 of the patients who harboured only yeast-like organisms 60 had symptoms of pruritus and discharge C. albicans was found in 52 per cent. of those who were symptomatic.

*Yeast-like organisms of the skin* A great number of yeast like organisms have been associated with a great variety of dermatoses and many have been assigned as aetiologic agents to various cutaneous afflictions The results obtained from a study of the occurrence of yeast-like organisms on the normal skin have been extremely variable.

WACHOWIAK *et al* found no yeast like organisms on normal skin. BIZZOZERO and CAO found them widespread. GREENBAUM and

KLAUDER found 33 per cent. of normals positive JESSNER and KLEINER found 59 per cent. FALCHI found 65 per cent. of 57 individuals positive STAEHLIN *et al* reported 82.8 per cent. positive and BENHAM found 72 per cent positive. BENHAM and HOPKINS were not able to isolate C. albicans from normal skin, but found it in pathologic skin cases, while other Monilias appeared in both conditions. They concluded therefore, that C. albicans is the only pathogenic member of the Monilia group

FISHER and ARNOLD investigated 577 persons in their survey concerning the yeast flora of normal skin and mucous membranes. Seventy five per cent. of adults and 52 per cent. of children were found to harbour one or more strains of yeast-like fungi. The vagina of normal pregnant women was 24 6 per cent. positive and from gynaecologic complaints, 11.3 per cent. positive. Gastric contents were 66 6 per cent. positive, and normal faecal specimens 38 4 per cent. positive Sputa of tuberculous patients were 35 per cent. positive. The organisms isolated were species of the following groups Saccharomyces, Cryptococcus Monilia and Mycodermata no Endomyces were isolated. No C. albicans strains were found on normal skin, but were isolated from the mucous membranes gastric contents, and faeces under normal conditions



775 Intertriginous seborrhoeic dermatitis of the submammary area with secondary monilial infection.

More recent investigations (MONTGOMERY) confirmed the results of previous findings on a statistically significant material, concerning the occurrence of yeast like organisms on normal skin and intact mucous membranes At the New York Skin and Cancer Unit from 1935 to

1942 inclusive, 1 773 positive cultures of C. albicans were made. The *fingernails* as one would expect, had the highest incidence of positive cultures—31 6 per cent. It is also interesting to note the high incidence on the *tongue* (19 4 per cent. this is not surprising since the tongue is in continuous contact with the oral mucosa) in the *groin* (15.3 per cent.) and on the *feet* (10 9 per cent) *Other intertriginous areas* such as the hands, breasts, axillae, anus, ears and so forth, made up the remaining 22.8 per cent.

## OCCURRENCE OF YEAST-LIKE ORGANISMS ON THE SURFACE OF SKIN AND MUCOUS MEMBRANES UNDER PATHOLOGICAL CONDITIONS

Yeast like organisms are ubiquitous in nature, in practically every climate. Results of statistically significant investigations prove that they are constant inhabitants (commensals) of the mucous membranes



776. Intertriginous oozing seborrhoeic dermatitis which yielded in culture streptococci and yeast-like organisms.

(oral cavity gastrointestinal tract, vagina) and the normal skin surface including the nail organ. In well-being, the normal *ecology** of the microbiological flora on skin as well as on the mucous membranes keeps an admirable balance among the multitude of the various species.

However when this *ecologic balance* is disturbed by disease, *e g* diabetes, the vaginal mucosa as a natural nutrient soil for its microflora may automatically change in a direction which favours the luxur

*"Ecology" is the science of the relations of organisms to each other

iant growth of yeast like organisms, at the expense of other species. This profuse, uninhibited growth of yeast like organisms will create the clinical picture of *monilial vaginitis*. In the case of *tropical sprue* a nutritional deficiency probably due to chronic dietary vitamin-B complex deficiencies, the normal ecologic balance of the intestinal flora is profoundly disturbed because of the changed nutrient soil, so that the yeast like organisms come to prevail at the expense of all other organisms



777 Impetigo of the face associated with yeast-like organisms. Note blepharitis.

*(Simons Amsterdam)*

## DISTURBANCE OF THE ECOLOGIC BALANCE BY ANTIBIOTICS

The ecologic balance of the intestinal flora can also be changed, even fatally by means of our newer antibiotics such as aureomycin, chloramphenicol, terramycin In this instance, it is not the change in the nutrient soil which will cause the disturbance. These newer antibiotics simply eliminate both the Gram-negative and the Gram-positive intestinal bacterial flora, creating a "vacuum The yeast like organisms may expand in this vacuum" without a natural check they may gain

an unprecedented invasive power, and may even break into the circulation, causing a *fatal monilial septicaemia*

Recent observations of WOODS *et al* clearly illustrate the mechanism of this alternative. They encountered a sizable number of cases of "clinical moniliasis" in most of which the disease was apparently a direct sequel to antibiotic therapy The first group of patients regularly encountered were those with sore mouth, hairy tongue, perlèche or the clinical picture of thrush, resulting from the local use of penicillin or aureomycin (as sprays, troches, soluble tablets or powders) in the oropharynx. A similar observation was made in smaller group of patients in whom persistent diarrhoea developed after therapy with penicillin, aureomycin or chloramphenicol. In these patients C. albicans was found growing abundantly in the stools. These authors cases have fallen into three groups (a) infection of the oropharynx and oesophagus (b) infection of the intestinal tract with diarrhoea, and (c) pulmonary moniliasis.

The in vitro experiments of WOODS *et al* revealed that there was no evidence that any of these antibiotics *either increased or suppressed* the rate of growth of C. albicans. The effect of change in pH on monilial growth, resulting from alteration of bacterial flora by the antibiotics, was not seriously considered as cause of monilial overgrowth, largely on the basis of the observations of KARNAKY *They considered the suppression of the normal intestinal bacterial flora the most important single factor responsible for the luxuriant growth of C albicans following the use of antibiotics* PAPPENFORT and SCHNALL came to a different conclusion. A significant number of patients who received the form of aureomycin hydrochloride prepared for oral administration showed signs of luxuriant growth of C. albicans. This effect was observed from several different lots of the drug They observed that aureomycin hydrochloride for oral administration stimulated the growth of Candida albicans, Cryptococcus neoformans, and Saccharomyces cerevisiae in vitro. They assumed that the growth-stimulating factor of this aureomycin preparation, according to its properties, is probably not the same as the antibiotic factor

REICHE's recent observation illustrates another mechanism of the overgrowth of C. albicans on a diseased skin surface. H reported three cases in which "genitocrural dermatitis" (most probably seborrhoeic dermatitis) developed following chloramphenicol, terramycin and aureomycin medication He believed these cases were due to decreased tissue resistance to C. albicans, caused by sensitization to these antibiotics. However, the type of reaction these patients produced is not that observed after true sensitization to these antibiotics. Drug eruption and the biotropic effect of a drug are two entirely different manifestations of different pathological mechanisms (BESZONYI). On a changed nutrient soil C. albicans may show a more luxuriant growth as *saprophyte* but not as an aetiologic agent.

Candida albicans is a common saprophyte of the normal mucous membranes the skin and the nail organ. As long as these tissues are normal, the C. albicans will not cause any pathologic manifestations. However there are a number of pathologic mechanisms which will permit a luxuriant overgrowth of this yeast like organism on mucous

membranes diseased skin and nail organ without its having anything to do with the underlying specific, pathologic tissue changes. The clinical appearance of its luxuriant growth (oral and vaginal thrush, etc.) is fallaciously considered as the true primary pathologic process. The luxuriant growth of C. albicans on mucous membranes and the skin is only an *indicator* that the tissues have undergone specific pathologic changes (malnutrition, severe vitamin deficiencies, diabetes etc.) which have permitted the luxuriant growth of this organism. *Wherever the C. albicans appears on the surface of mucous membranes, skin or nail organ it remains a saprophyte; its visible clinical manifestation (e.g. thrush)—a saprophytosis.* *

Yeast like organisms are also among the commonest *mesoparasites* on the oozing inflamed human skin. The exuding serum of inflammatory skin lesions is an ideal nutrient medium for these organisms. Since they can be easily seen in smears from the oozing surface stained or unstained, and since they can just as easily be cultured, they set a dangerous trap for all those who unguardedly engage in research for feasible aetiologic agents in dermatoses of unknown aetiology.

## SYMPTOMATOLOGY

For didactic purposes it seems to be advantageous to discuss "moniliasis" under the following headings (1) moniliasis of the mucous membranes (2) systemic moniliasis (3) moniliasis of the skin and (4) moniliid or levurid.

### 1 MONILIASIS OF THE MUCOUS MEMBRANES

(a) *Thrush* (Soor muguet)

This is probably the most commonly recognized clinical form of this condition. It appears in grayish white or creamy patches of different

*Saprophytosis (saprophytia), a term introduced by UNNA, designates those afflictions of the skin in which micro-organisms of any kind (saprophytes) vegetate upon its surface without inciting any *pathologic tissue changes*. According to the definition they do not cause any but *mechanical changes* in the structure of dead or necrobiotic tissues upon which they vegetate. Further stipulations of this definition are that they may not produce any kind of exotoxins, and do not elicit any sort of progressive or regressive tissue changes. UNNA considered under saprophytosis (1) pityriasis versicolor (2) erythrasma and (3) piedra. In that sense, I should like to term "thrush" as a saprophytosis of the mucous membranes.

are on the mucous membrane of the oral cavity (buccal, gingival, lingual, pharyngeal). They can easily be wiped off leaving a smooth, red, shiny surface. *But it is not a primary disease*." It may appear in debilitated, marantic infants in whom the oral mucosa has lost its anatomic integrity and physiologic resistance, due to debilitating disease of any kind. The same holds true of elderly persons suffering from chronic debilitating diseases and from the so common malnutrition, and nutritional deficiencies (glossitis in vitamin-B deficiency, gingivitis in vitamin-C deficiency for instance). From the oral cavity the thrush



778 Thrush, the clinical appearance of the luxuriant growth of monilia is usually fallaciously considered as the primary process.

*(Vanbreuseghem – Antwerp)*

may spread per contiguitatem to the pharyngeal and oesophageal mucosa.

There is no "acute" or "chronic" type of thrush (BECKER and OBERMAYER). The organisms of thrush, C. albicans, spread with luxuriant growth only on *mucous membranes injured in their integrity and resistance*. As was already explained, either the nutrient soil (the mucous membrane) or the normal ecology of the microflora must be profound-

ly disturbed, to make possible an uninhibited growth of an almost constantly present saprophyte. Whether the process be acute or chronic depends entirely on the nature of the *underlying condition* and not on the continued presence of the thrush fungus.

A condition similar to oral thrush may appear on the vaginal mucosa (*monilial vaginitis*) when it has been chemically changed as a nutrient soil, *e.g.* in diabetic females or by destruction of the ecologic balance of the normal vaginal flora, *e.g.* by overtreatment with chemicals injurious to the mucous membrane.

In these instances it is completely irrational to treat the fungus infection. The basic diseases such as malnutrition, vitamin deficiency, diabetes have to be treated. As soon as the normal ecology of the microflora of the oral and vaginal mucosa is restored, the C. albicans will cease automatically to be able to grow luxuriantly and the thrush will disappear.

(b) *Perlèche* (cheilosis, angular stomatitis)

This disease of the mucous membrane of the commissure of the lips is characterized by more or less deep cracks, redness and oozing. The mucous membrane may appear thickened, bluish white in colour (mother-of-pearl) and macerated. It occurs mainly in childhood and in the aged. Two organisms were incriminated as aetiologic agents in the past: (1) Streptococci and (2) C. albicans. However *perlèche is not a microbial process*. It is a manifestation of vitamin-B complex deficiency (STANNUS, SEBRELL, URBACH).

Streptococci, if present, may cause impetiginization. Yeast like organisms are without any aetiologic significance. Even if present they do not require any special attention. As soon as the vitamin B level is restored the cracks heal, the oozing stops and the yeast like organisms will disappear or again become innocuous saprophytes.

Perlèche, being a manifestation of a vitamin deficiency is neither infectious nor contagious. "Epidemics" described in schools and orphanages (FINNERUD) can be easily understood because of the prevalence of widespread malnutrition in the underprivileged strata of the (school) population and in orphanages.

## 2. MONILIASIS OF THE INTEGUMENT

### (a) "*Erosio interdigitalis blastomycetica*"

This was first described by FABRY in 1917 It is characterized by the presence of a white or red, oozing macerated area covering the webs of the fingers or toes and extending a short distance on the sides of the fingers. Since direct smears from the oozing surfaces and, even more so scrapings in culture tubes revealed pure cultures of yeast like organisms, FABRY assumed the "blastomycetic" aetiology of this condition The pathogenesis of this erosion is the same as of those deep-



779 Erosio interdigitalis blastomycetica, actually secondary monilial infection of one localization of cheiropompholyx.

seated sago-grain-like blisters on the palms and soles, but, due to the thinness of the epidermis in the webs and in the roof of these blisters they are evanescent. They break at the slightest pressure, leaving a shiny red, usually oozing surface. *Erosio interdigitalis blastomycetica" does not exist as an aetiologic entity* To this author it is *one* localization of *pompholyx* secondarily infected by monilia (BENEDEK)

It is commonest among members of trades and occupations (house keepers, dishwashers, laundry women) whose hands are exposed too much to soap and water Thus author had 8 patients (2.1 per cent.)

ly disturbed to make possible an uninhibited growth of an almost constantly present saprophyte Whether the process be acute or chronic depends entirely on the nature of the *underlying condition* and not on the continued presence of the thrush fungus.

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In staphylococcic onychia and/or paronychia there are no nail changes at all. Acute onychia and paronychia are caused mostly by Staphylococci, less frequently by Streptococci or Escherichia coli. They are the *felon* or *whitlow* which are accompanied by excruciating pain, throbbing in the finger etc. The process may be so intensive that the nail plate is quickly undermined and the affliction can only be stopped and cured by incision and often, by surgical removal of the nail.

As in "erosio interdigitalis blastomycetica" in "*monilial*" paronychia the erroneous "aetiologic diagnosis was based on smears and/or cultures of the thin creamy pus exuding from underneath the inflamed and swollen nail wall. This fluid may contain innumerable yeast like organisms like the "erosio" on the webs of fingers and toes. They are *nosoparasites* without any aetiologic significance

### (c) "*Intertrigo*"

In the parlance of descriptive dermatology "intertrigo" (synonym erythema intertrigo eczema intertrigo chafing) is the reddening and oozing of two adjacent skin surfaces in close contact with each other, as in the axilla, groin, genitocrural, and intergluteal regions, inter mammary and submammary surfaces in women with pendulous breasts. The heat, rubbing sweating and subsequent maceration are important eliciting factors in intertrigo. In baby's "*diaper rash*" the irritating effect of urine and faeces are aggravating factors. Profuse vaginal discharge of any cause may elicit a genitocrural intertrigo

The detritus masses on the oozing skin surface (sweat, serum, epithelial debris) form an excellent nutrient soil for nosoparasites—Streptococci and Monilias, in particular.

Yeast like organisms, C. albicans or any other species, thus are without *aetiologic significance* on intertriginous surfaces.

### (d) *Moniliasis following continuous baths and wet dressings*

This syndrome was originally described by JACOBI as "*water-bed trichophytosis*" and later by KUMER as "*thrush infection of the skin*" The same syndrome was also observed following prolonged wet dressings. The establishment of C. albicans on the surface of the macerated skin is not the primary cause of the ensuing dermatitis The continuous bath and the continuous wet dressing produce a constant irritation on the exposed areas of the skin preparing areas of lesser resistance

for the development of *seborrhoeic dermatitis* In the detritus of the macerated skin hosts of nosoparasites may vegetate without any bearing on the basic inflammatory process.

JACOBI most interestingly clearly visualized the development of this "moniliasis"* He underscored the fact that the germs (C. albicans) can vegetate on the skin surface *only after* the epidermus undergoes a maceration of the highest degree particularly in cachectic individuals. *Under these conditions* they may multiply and they may also acquire a virulence of low degree However when the skin becomes dry again the whole process ceases to exist.



781 Seborrhoeic dermatitis of the genito-crural region which yielded streptococci and yeast like organisms for which reason it may easily be called moniliasis.

(c) *"Generalized cutaneous moniliasis"*

There is an observation of ROCKWOOD and GREENWOOD (1934) on "monilial infection of the skin" with fatal outcome, which is quoted repeatedly in the literature However this case by signs symptoms, course, duration and autopsy finding is not acceptable as an example of systemic moniliasis

The patient white American, aged 51 had a generalized erythemato-squamous eruption of the skin already of one year ed ration when first observed. The disease was said to ha begun in the mouth, later involving the palms, then the nail

* JACOBI used the term "trichophytosis" but the plat enclosed with hi paper reveals beyond doubt that what he saw and cultured was C. albicans

folds as paronychias, the face, neck, the axillae, groin, the lower part of the abdomen and the upper part of the thighs. Nearly all the nails were thick opaque and yellow The palms were thick and yellow almost verrucous in places.

The detailed clinical description of this patient and the two photographs (one frontal view of the body one palm) permit only one clinical diagnosis seborrhoeic dermatitis complicated with pompholyx of the palms and nail organs.

Of the laboratory findings the continuous high lymphocytosis was noteworthy Blood cultures were consistently negative. On two widely separated occasions the patient's serum failed to agglutinate his own organism (C. albicans) cultured from the tiny abscesses of the skin.

The patient died about two and a-half years after onset of the condition, completely emaciated. At autopsy all the internal organs were found to be normal and, in particular free from any yeast-like organisms.

In view of these facts the pathologist's assumption was that the fatal outcome was caused by *absorption of toxins* of C. albicans This opinion was supported by no evidence whatever.

In ROCKWOOD and GREENWOOD's patient one fact stands out – he died without an exact clinical or pathologic diagnosis. That the oral thrush progressed from the mouth to the larynx and oesophagus per contiguitatem is not unusual in a patient undergoing progressive cachexia. That he developed abscesses containing monilial organisms on a already severely damaged and inflamed skin has nothing to do with his undiagnosed primary disease

KRAUSPE (1927) contributed one of the best and most comprehensive studies about the biology of Candida (the thrush fungus) and about the pathogenesis of thrush infection. He demonstrated that C. albicans does not produce exotoxins in culture or in the tissue fluid of rabbits infected intravenously with this organism.

In this connection we have to discuss cases of *granulomatous moniliasis*" The "causative" organism was always erroneously identified as C. albicans. HAUSER and ROTHMAN described a case of a white boy aged 7 under the diagnosis of "monilial granuloma"

Many of the characteristic individual papules on the forehead and cheeks were surmounted by cutaneous horn-like structures. The underside of the crusts showed prominent follicular plugs. The lips were swollen crusted and deeply fissured between the crusts. The gingivae were inflamed and swollen. The scalp lesions healed with irregularly shaped atrophic areas, with partial loss of hair and follicular pores. The nail plates of both thumbs and the left index finger were rough, opaque and irregularly heaped-up into large pyramidal structures. The mycological diagnosis of "moniliasis" was based solely on findings of fungous elements (C. albicans) in *superficial scrapings of the stratum corneum* The histological findings in biopsy specimens were characterized by hyperkeratosis and acanthosis in the epidermis. The

corium was filled with a dense infiltrate consisting of lymphocytes, plasma cells, polymorphonuclear leukocytes and foreign body giant cells. The infiltrate extended downward to the subcutis and was perifollicular and periglandular in some areas. "Fine filaments, which were probably hyphae, were seen in the stratum corneum."

The clinical and histological description (hyperkeratotic plugging, atrophy of the follicle, nail involvement) points to the manifestation of a severe vitamin-A deficiency; the swollen and inflamed gingivae make the diagnosis of scurvy most probable; the continuous formation of cutaneous horns may indicate a substantial ectodermal defect. Moreover, the "granulomas" were at all times free of fungous elements.

HAUSER and ROTHMAN collected 13 other cases of "monilial granuloma"



782 Test tube with colony of Candida albicans with "inverted fir tree appearance" on beer wort agar (3 weeks–20° C).

from the literature. All diagnoses were based solely on findings of monilial elements in *superficial scrapings*.

The case reported by MOORE as "granulomatous moniliasis resembling Gilchrist's disease" is most probably, in its clinical appearance and histological picture, Gilchrist's blastomycosis.

Both HAUSER and ROTHMAN, and MOORE undertook animal inoculations, to offer some semblance of fulfilment of one of KOCH's postulates in proving the pathogenicity of the organism in question; the former used a rabbit which they inoculated intravenously. The animal died in five days. At autopsy both kidneys were swollen and studded with abscesses. The latter used mice inoculated intraperitoneally. They died within 2 to 16 days after infection. The mice showed tubercle-like, cream-coloured nodules in the intestines, pancreas, kidneys, spleen and liver.

These animal experiments, it should be understood, do not permit any inference concerning the organisms' pathogenicity in humans. They characterize only the organism itself and its pathogenicity in the *animal species* used.

One can only conclude that all "infectious granulomas" like those we find in blastomycosis, coccidioidomycosis, etc. and which have hitherto been described, were not caused by C. albicans. If C.

albicans can invade the human organism, it causes only *abscess formation* as in experimental animals like the rabbit and mouse. Another characteristic feature of C. albicans, if invasive, is that it causes extremely quick destruction in the sensitive animal as well as the human body. The author's numerous experiments with monilias in rabbits by the intraperitoneal and intravenous route led to quick death and formation of innumerable abscesses in all parenchymatous organs, particularly in the liver and kidneys. In no case was the formation of infectious granulomas seen. In those cases where C. albicans was found, it is most probable that the investigator was too early satisfied with the discovery of the non-causal but coexistent micro-organism.

## 1. SYSTEMIC MONILIASIS

The existence of systemic moniliasis is an entirely different problem.

The best true examples of this condition are those fatal cases which developed in infants and children after long continued administration of certain antibiotics, such as aureomycin and chloromycetin. In principle any antibiotic can become the eliciting cause of an excessive invasiveness of C. albicans. By destroying the normal *ecologic balance* of the microflora of the intestinal tract an ecologic "vacuum" is created. This "vacuum" permits the C. albicans to grow uninhibitedly and to gain excessive invasive power. Thus, it may break into the circulation and produce a true monilial septicaemia.

Fatal C. albicans infections as a sequel of prolonged aureomycin administration were already reported by ZOLA K. COOPER at the 1950 meeting of the American Academy of Dermatology and Syphilology with demonstration of pathological specimens of parenchymatous organs, fully invaded by this yeast like organism. Fatal, systemic, monilial infections were also reported by HARRIS (aureomycin) and WILLIAMS (chloramphenicol). In the instances in which autopsy was performed the internal parenchymatous organs, liver, lungs, and kidneys were studded through and through with superficial and deep micro-abscesses filled with these organisms. The picture is exactly the same as in the experimental infection with C. albicans in the rabbit, the most sensitive laboratory animal for this purpose.

At present there is no known therapy in systemic moniliasis. The

fatal cases reported may serve as a stern warning against excessive and unduly prolonged administration of all antibiotics.

*Broncho-moniliasis*

One of the most difficult diagnostic questions is to decide the role played by C. albicans in cases of the so-called "broncho-moniliasis" In most instances monilial organisms will be only secondary invaders in the presence of a primary disease of the bronchial tree and the lungs of entirely different aetiology like chronic bronchitis, tuberculosis coccidioidomycosis, etc.

This author had the opportunity to study for long period two cases of



783 Moniliasis found in the oesophagus

(*Lignac – Leiden*)

coccidioidal granuloma of the l ngs (1) a soldier aged 23 and (2) a woman aged 30 in whom the sputum contained beside great numbers of typical spherules of Coccidioides immitis at least thirteen different species of cocci and bacilli, and C. albicans However the cutaneous abscesses developed by these patients contained only the really causative Coccidioides immitis. This author believes that the existence of a true "broncho-moniliasis" can be decided upon only on the autopsy table C ltures and smears in vivo do not prove aetiologic significance.

## 4. MONILIID (HOPKINS) LEVURIDE (RAVAUT AND RABEAU)

The synonymous terms *moniliid* and *levuride* were formed in analogy with the term *epidermophytid*. They are supposed to mean certain skin eruptions caused by yeast-like organisms transported from a "focus of infection" (*e g* gastrointestinal tract) by the way of the circulating blood onto the allergic skin

In connection with this hapt r consult Chapt rs 61 92 and 93

Curiously enough, HOPKINS and RAVAUT never claimed either that they were able to culture yeast like organisms from the circulating blood in their moniliids (HOPKINS) and levurides (RAVAUT and RABEAU).

HOPKINS emphasized that the repeated failure to demonstrate C. albicans in most of the cutaneous lesions seemed to rule out a "true" moniliasis of the skin. The fact that skin lesions could be reproduced by the injection of sterile extracts of C. albicans suggested another interpretation, viz., that they were produced by the reaction of sensitized areas of the skin to specific substances absorbed from the heavily infected gastrointestinal tract. In other words, that they were "moniliids."

He underscored the fact that RAVAUT and RABEAU studied lesions described by different authors under diverse terms "parakeratose" (BROCQ), "eczématide" (DARIER), "pityriasis rubra disséminée" (BAZIN) or "seborrhoeic eczema" (UNNA).

The essence of the investigations of RAVAUT and his co-workers can be summed up as follows. They observed patients with seborrhoeic dermatitis who had dry lesions on the body and weeping lesions in the typical intertriginous areas. They could easily culture yeast-like organisms (they never were identified by them as to their species) from the weeping surfaces, but the scrapings of the dry areas usually remained sterile.

Injections of suspension of heat killed yeast like organisms ("*levurine*")[1] often elicited an eczematous *local reaction* at the spot of the injection and a *focal reaction* characterized by a flare-up of the distant cutaneous eczematous lesions.

In some cases the intradermal injection of levurine provoked cutaneous lesions very similar to those of *pityriasis rosea* (RAVAUT and LONGHIN 1930) another time the lesions revealed characteristics intermediate between those of *seborrhoeic dermatitis and psoriasis vulgaris* (RAVAUT and RABEAU 1929).

RAVAUT and CIVATTE's histological examination demonstrated that the microscopic structure of these secondary lesions was that of banal seborrhoeic dermatitis or psoriasis. DARIER[2] was in full agreement with their findings.

RAVAUT and co-workers created the fantastic term of "*streptococcide*" because in some cases of retroauricular and axillary weeping seborrhoeic dermatitis streptococci and no yeast-like organisms were cultured. They concluded that "streptococcid" may develop on the same pathogenetic basis as the "levuride."

Interestingly HOPKINS could elicit an exacerbation of seborrhoeic dermatitis only by a suspension of heat killed C. albicans. Similar

[1] Levurine and "oidiomycin" designate exactly the same principle a suspension in physiologic salt solution of heat-killed heterogenous yeast like organisms.

[2] "Les lésions histologiques de ces lévurides stériles constatées par Civatte et par moi étaient nettement celles d'une eczématide. Ainsi P. Ravaut a non seulement constaté l'action pathogène et le pouvoir allergisant de ces levures, mais il a pu [illegible] avec un extrait levurine, à sa[illegible] [illegible] la toxine correspondante produire expérimentalement des lévurides de type eczématide [illegible] stables et stériles." (DARIER).

tests with trichophytin and with extracts of M. parapsilosis, M sitophyla, Alternaria, Trichothecium, Trichoderma and Staphylococcus aureus as well as with a control of sterile broth, gave negative results.

BAILEY and GOLDMAN investigated the cutaneous reactions with "purified" oidiomycin (levurine – RAVAUT). RAVAUT demonstrated that oidiomycin (levurine) reacts in almost every case within 24 hours but he regarded this as a "false" reaction. He considered only the late "true" reaction, which he interpreted as an indication that the patient is infected with pathogenic yeast like organisms. He found this particularly true in patients who also showed "levurides" This reaction might be described as a "flare up" occurring as it does several days after the "false" reaction.

Since yeast like organisms occur on the skin of nearly every person, BAILEY and GOLDMAN considered the reaction as analogous to the positive tuberculin reactions found in most adults who live in thickly populated centres If this last supposition is correct, they reasoned, the true" reaction of RAVAUT indicates nothing more than a particularly stormy false" reaction.

BAILEY and GOLDMAN prepared a "purified oidiomycin" in order to compare the results with those of RAVAUT who worked with "unpurified oidiomycins Every patient gave a positive reaction in from 24to 48 hours after injection of these purified oidiomycins. In spite of the process of purification" they obtained the same false" reactions as RAVAUT They could not decide whether these reactions were non-specific in spite of the process of purification or whether all persons tested were hypersensitive to purified oidiomycin because of latent infection

Intertriginous areas like the retroauricular axillary submammary and other regions are not a primary focus" and the "dry" areas do not represent "secondary amycotic" foci an id" eruption. The difference in the superficial, nosoparasitic flora depends entirely on the different quality of the nutrient soil.

**THERAPY**

The thorough analysis of moniliasis and moniliid" dissolves this non-existent aetiological" group into a few truly aetiological entities The correct therapeutical measures must be directed against the aetiologic agent

Since *perlèche* is a definite manifestation of vitamin-B complex deficiency the therapy should consist of the administration of brewers yeast tablets with one or two tablets three times daily for a prolonged period of time. When there is a secondary impetiginization (as is often present in children) a local antibiotic like Tyroderm (tyrothricin) will be promptly effective

*Thrush* (Soor, muguet) was found to be a saprophytosis Its local treatment is valueless. Since it appears in individuals with nutritional deficiency or malnutrition, *these factors* have to be removed Then, the normal ecology of the microflora restored, the C. albicans will disappear. Similarly in vaginal thrush ("monilial" vaginitis) the under lying disease, diabetes, banal vaginitis, etc., has to be treated and not the *C albicans* which, in its luxuriant growth, is only an *indicator* of some basic disturbance not connected with the fungus at all.

As far as oozing surfaces ("intertrigo") are present locally boric acid wet dressing is indicated. In any age, infant or adult, to prevent the development of an oozing seborrhoeic dermatitis (intertrigo) the following powder is recommended

| | |
|---|---|
| tannic acid | |
| boric acid | |
| salicylic acid | aa *2.0* |
| talcum | ad *100.0* |

In this compound the tannic acid is the most important ingredient. It certainly counteracts the macerating action of the continuous sweat secretion which loosens the stratum corneum. It tans hardens it, and thus gives the greatest protection Whether salicylic acid is absolutely necessary in this formula is debatable. However, it was kept in this compound as an antibacterial agent, and particularly to maintain the low pH in the acid mantle of intertriginous surfaces, along with boric acid as a mild astringent and disinfectant.

Proprietary powders and ointments like propionate-caprylate mixtures (sopronol) and zinc undecylenate (desenex) powder or ointment have been recommended more recently in tremendous advertising campaigns. This author heartily agrees with MITCHELL that these compounds are of very little value for any purpose and is absolutely

against the harmful, and wasteful polypragmasy of prescription writing used by many dermatologists. It is harmful, because it frequently leads to an overtreatment dermatitis wasteful, because it places an unjustifiable financial burden on the patient.

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# TINEA CAPITIS ET BARBAE

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## INTRODUCTION

Ringworm of the scalp is a fungous infection caused by several species of the Dermatophyte genera *Microsporum* and *Trichophyton* The condition is often chronic and slowly progressive and is difficult to treat. Children are more susceptible than adults and only certain species can attack adult scalps. The lesions are infectious and at least one species of fungus can cause widespread epidemics. During the years since World War II tinea capitis has been relatively common in many temperate countries. It appears to occur somewhat less frequently in the tropics, and in some areas, such as the South Pacific it is extremely rare (MARPLES).

The appearance and progress of the infection depends to some extent on the aetiological species and will be discussed under the headings of the invading organism. There are some signs however, which are common to all infections. In general the condition appears as a patchy scaling baldness, the hairs being dull and friable and breaking off flush with the scalp or a little above it. The reaction of the host tissues may be either negligible or of increasing severity up to an extensive swelling, bogginess crusting and even a suppurating condition. In children showing a patchy baldness the diagnosis of tinea capitis should always be excluded in laboratory examination, before other conditions are considered.

## INFECTIONS CAUSED BY THE GENUS MICROSPORUM

### SYMPTOMATOLOGY

The lesions may be single or numerous They appear as scaling bald patches, varying from about 5 millimetres to several centimetres in diameter Occasionally almost the whole scalp may be involved, and in rare cases the eyebrows and even the eyelashes may be infected.

Infected hairs lose their normal lustre and appear grey and crusted, breaking off about 5 millimetres above the scalp surface. They are loose and friable and easily removed for microscopic or cultural investigation.

The inflammatory reaction varies to some extent with the invading



784 Numerous squamous patches of the facial skin and scalp due to microsporum infection.
*(Orig G Castro-Bela Hartzmann)*

species but there is no rigid correlation, and any of the species can cause a considerable host response Generally however lesions caused by *Microsporum audouini* show little reaction, while those caused by *M canis* and *M gypseum* show more tissue response even to the extent of forming a kerion, a painful raised red moist pustular condition. Kerion may be present from the onset of the infection or may develop during the course of treatment with topical applications.

Infections due to *M audouini* untreated, are slowly progressive but

almost always clear up spontaneously at puberty. Those due to *M. canis* and *M. gypseum* tend to recover spontaneously even before this age is reached. In New Zealand three clinical patterns of infection due to *M. canis* have been observed (MARPLES). The lesion may remain single throughout the clinical course; it may produce a few small satellites, but remain localised, or about four to six weeks after the onset, there may be a sudden generalized spread involving the greater part of the scalp.

The site of the lesions also varies with the aetiological species. SCHWARTZ and his co-workers found that infections due to *M. audouini* occurred most commonly on the occipital area. Those due to *M. canis* and *M. gypseum* at least in New Zealand develop equally readily on any part of the scalp.

## EPIDEMIOLOGY

The genus *Microsporum* is the predominant cause of tinea capitis in most temperate countries. It is less commonly found in tropical areas although VANBREUSEGHEM described a new species *Sabouraudites (Microsporum) langeroni* which is common in central Africa.

The species show an interesting geographical distribution, different ones predominating in different areas within a country. LEWIS and HOPPER recorded an almost equal incidence of *M. audouini* and *M. canis* in New York; in midwestern and eastern states *M. audouini* predominated, while in California *M. canis* was much more frequently encountered. *M. canis* appears to be rare in most parts of Europe, but DEGOS and RIVALIER in Paris recovered a large proportion of *M. canis* strains, and THOMAS, LENNOX and DUNCAN reported an increasing incidence of *M. canis* infections in Great Britain, this species predominating in some areas. In New Zealand it is the major cause of scalp ringworm. *Microsporum gypseum*, the third established species, appears to be rare in most parts of the world except South America.

The epidemiology of microsporosis again depends on the causal organism. *Microsporum audouini* is an anthropophilic species, easily transmitted, and causing widespread epidemics among children in schools and other institutions. Boys are much more commonly infected than girls. BENEDEK records that 86.4% of his subjects were boys and other authorities have found the same preponderance both

in the United States and in Europe. Widespread epidemics of tinea capitis have been reported in the post war years. SCHWARTZ *et al* have suggested that the fungus is spread by barbers clippers, and



785 Slide culture of Microsporum gypseum showing numerous thin walled macroconidia.

*(Marshall-Dowda)*



785a Thick walled macroconidia of Microsporum canis.

*(Marshall Dowda)*

BENEDEK has stressed the importance of examining contacts of known cases, *since in some of these the lesions may be so insignificant that* the subjects can be regarded as carriers Adult infections of the scalp are extremely rare but several authorities have reported isolated cases. Domestic pets are not involved in the spread of the condition

and laboratory animals are rarely susceptible to an experimental infection.

The epidemiology of *Microsporum canis* presents a very different picture. The reservoir for this infection resides in domestic pets and the virulence of a strain is rapidly reduced after a few human transmissions. *Small family outbreaks occur but it is rare for M canis to* cause epidemic ringworm. Young animals are more susceptible than old ones, and may have a widespread area of coat involved, even when no obvious lesions are present. Patients often give a history of contact with an animal and it is important to examine the domestic pets as well as the human contacts when tracing the source and extent of an outbreak. Only about twice as many boys as girls are infected (WALKER and MARPLES) The condition tends to clear up even in the absence of treatment. In this area, where *M canis* predominates, a distinct seasonal fluctuation has been observed over the past five years. New cases occur in steadily increasing numbers from early autumn to midwinter and then decrease until midsummer, at which time new infections are rarely encountered. Scalp lesions in adults seldom occur, although PIPKIN suggests that their incidence is greater than is generally realized, but tinea corporis in the adult members of the family associated with tinea capitis and corporis in one or more children is a common finding Cats, guinea pigs and other laboratory animals are susceptible to experimental infection.

Little is known of the epidemiology of *Microsporum gypseum* Lesions due to this organism usually show considerable inflammatory reaction and clear up rapidly Animals are spontaneously infected and provide a reservoir of infection. In this area the species has been found more commonly in puppies than in kittens. It seems likely that the species is of low pathogenicity to man, since even family outbreaks are rare.

## MYCOLOGY

The Wood light is of the greatest value, both in the diagnosis and control of scalp microsporosis Spores formed during parasitic growth of *Microsporum* cause the invaded hairs to fluoresce a brilliant green. This facilitates not only the determination of the extent of the infection but also the collection of material for laboratory examina

tion. In using the Wood lamp the following points should be noted

(a) Fluorescence does not become obvious until some little time after the onset of infection.

(b) In inflammatory lesions, the hair stumps may be buried and fluorescence can only be observed after their extraction.

(c) Occasionally strains of *Microsporum* which do not fluoresce are encountered

(d) Fluorescence pales during the course of treatment with topical applications and may be masked by the presence of medicaments.

Hence direct and cultural examination are of great value in confirming a doubtful diagnosis under the Wood lamp.

### DIRECT EXAMINATION

Hairs for microscopic examination should be collected and prepared as described for skin scrapings in Chapter 52. The fungus appears as a mosaic of small spores, encrusting the shaft of the hair. Hyphae running longitudinally inside the hair and traversing adjacent scales of skin are sometimes seen. APPEL and ANSELL have reported the occurrence of septate macroconidia in vivo but this is a most unusual finding and these large spores are almost always confined to the saprophytic life of the fungus.[1]

### CULTURE

The different species of *Microsporum* can only be identified in culture. For the preparation and identification of Microsporum cultures Chapter 52 should be consulted.

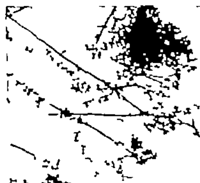
### INFECTIONS CAUSED BY THE GENUS TRICHOPHYTON

The classification of Trichophyton species is difficult and controversial. Both anthropophilic and zoophilic strains are found. These

[1] According to BENEDEK the so-called "macroconidia" is an animal cell and not of vegetable origin. The cells described in the parasitic stage of the genus Microsporum are typical of Henle layer of the internal root sheath of the hair. *Sabouraud* correctly recognized these spurious "macroconidia" as epithelial cells."

groups can be distinguished to some extent, by studying the arrangement of the fungal elements in infected hairs. The type of clinical lesion is also some guide to its aetiology but cultural investigation is the only reliable method of identifying the species

SABOURAUD divided the genus into three groups —*Endothrix* where the fungal elements are found entirely within the hair, *Ectothrix* where the fungus grows mainly outside the hair and *Neoendothrix* where the fungus is distributed both within and without the invaded hairs. These divisions cannot be relied on too rigidly but are a useful preliminary means of grouping the organisms. Pure endothrix strains are derived from human sources, while ectothrix strains commonly



786 Numerous microconidia arranged along hyphae of Trichophyton sulfureum. *(Marshall-Dowden)*

parasitize domestic animals, from contact with which man is infected Neoendothrix strains are transitional, and can often be experimentally transmitted to animals

## SYMPTOMATOLOGY

In general the lesions caused by endothrix species are chronic with little inflammatory reaction. The hairs are usually broken off at the scalp surface and the roots are firmly attached and difficult to remove. This is especially true in the condition known as *black dot ringworm* caused mainly by *Trichophyton violaceum* Infections caused by ectothrix strains may show all grades of inflammatory reaction, the

most severe of which are designated kerion. Inflammatory granuloma may also be caused by *Trichophyton sulfureum tonsurans* In these conditions the hairs may be shed spontaneously or may be buried in the inflammatory debris and therefore difficult to obtain for laboratory procedures. *Trichophyton (Achorion) schoenleini* and occasionally other species may cause the condition clinically known as favus This condition occurs most commonly on the scalp and may be present as an irregular crusted area with loss of hair due to atrophy or more characteristically with cup-like protruberances known as scutula. Each of these develops round a hair follicle. The fungal mycelium growing in the deeper layers of the epidermis raises the more superficial layers above the scalp surface, and the scutulum, appears microscopically as a conglomeration of fungal hyphae and disintegrating epidermal cells. These structures which have a characteristic "mousy" odour are of considerable diagnostic significance, but do not exclude the need for cultural examination since *T violaceum* *T quinckeanum* and occasionally even *M gypseum* can cause clinical favus

EPIDEMIOLOGY

Species of Trichophyton are more commonly found as the cause of scalp ringworm in tropical and subtropical countries, but strains are recovered sporadically in all parts of the world. *T schoenleini* has a widespread distribution and causes a small proportion of infections in the United States (DOBES and other authorities) It occurs occasionally in England (WALKER) and is relatively common in some parts of Europe (DEGOS and RIVALIER MATILLA and PENA YANEZ)

It has also been reported relatively frequently in Teheran, by ANSARI and FAGHIH

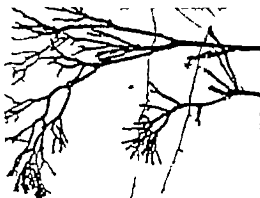
Most infections clear spontaneously at puberty or even earlier but occasionally infections, contracted usually in childhood, may linger on into adult life. Infections of the favus type may last for many years and when finally eradicated may leave permanent scarring and baldness Infections of the kerion type are usually self limiting and self healing

Widespread epidemics of scalp ringworm are not often produced by species of *Trichophyton* Infection may come from a human contact suffering from tinea capitis corporis barbae or even occasionally

tinea pedis Frequently however the organism is transmitted through contact with horses or cattle, and several agricultural families in this neighbourhood have shown lesions of the glabrous skin among the adults and scalp lesions in the children.

## MYCOLOGY

Hairs infected with Trichophyton strains other than *T schoenleini* do not show green fluorescence under the Wood lamp but may be white, grey or bluish in colour Those infected with *T schoenleini* fluoresce



787 Favic chandeliers of T schoenleini.
*(Marshall–Dundas)*

green but the colour is duller and yellower than that seen in a *Microsporum* infection.

## DIRECT EXAMINATION

Hairs should be prepared for microscopic examination as previously described. In endothrix species the spores are found in columns inside the hair Neoendothrix strains may have spores both inside and outside the hair while in ectothrix infections the majority of the spores are on the hair surface In all three groups the arrangement of spores differs from that found in microsporosis, in that the spores have a definite linear arrangement. SKINNER and his co-workers believe them to be true arthrospores produced by the segmentation of a

hyphal strand Ectothrix fungi are further subdivided into two groups, large-spored forms, and small-spored with parasitic spores of about the same size as those found in *Microsporum* infections Hairs infected with *T schoenleini* show a reduced number of spores often of irregular shape, and, characteristically longitudinal air spaces splitting the shaft.

## CULTURE

Cultures should be inoculated as described for *Microsporum* Some species of Trichophyton are difficult to propagate and grow very slowly Identification of the species depends on both macro- and



788 Favus umbilicated scutula.

microscopic features of the colony For a description of the species of Trichophyton Chapter 88 should be consulted

## THERAPY AND CONTROL

Scalp ringworm may be very difficult to cure and a knowledge of the aetiological species is of great assistance in selecting the most suitable form of treatment Other factors to be considered are the age of the patient, the extent of the infection, the amount of cooperation likely to be obtained and the danger to other children. In general kerion and other inflammatory infections are readily controlled, while

those in which there is little host response are difficult to eradicate.

In chronic non-inflammatory lesions, it is essential to get rid of the infected hairs. This can be effected in three ways

(1) *Epilation by X-rays*

This method is the most satisfactory provided that the treatment is in the hands of a trained and experienced operator MACKEE describes details of the technique. Briefly by using suitable dosage with a standardized machine, the whole scalp is irradiated, using several



789 Favus scutula due to T. schoenleini.
*(Orr G Castle–Bela Hertzman)*

separate exposures. The hair begins to fall out about two weeks later, and the child becomes completely bald in a further two or three weeks. Inspection under a Wood lamp is advisable at the end of this period to ensure that all infected hairs have disappeared. If any remain they can be manually epilated. Care should be taken that during the process of epilation the hairs are not disseminated A 3% ammoniated mercury ointment should be applied daily after the exposure to X rays, and when the hairs begin to loosen the whole scalp should be shampooed daily

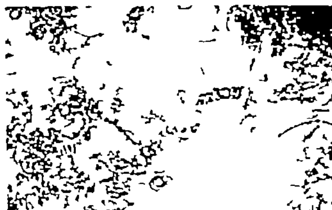
This form of treatment is particularly valuable in infections due to

### SYMPTOMATOLOGY

Tinea barbae is regarded as synonymous with mycotic folliculitis which may agminate into one or more painless nodose infiltrations. The hair is easily extracted from the follicle involved. The two distinct types are the purely *folliculitis* type, and the *kerion* or *sycosis type* is when nodules have been formed. Scarring is usual in both forms, although more conspicuous in the latter

### MYCOLOGY

In the majority of cases tinea barbae is due to *T mentagrophytes* The



791 Microconidia of T mentagrophytes.
(*Marshall–Dunedin*)

nodose type is most often due to infection with either *T mentagrophytes* or *T lanosum* while *Microsporum canis* *T violaceum* and *T purpureum* seem to cause the mild, follicular type.

For further data concerning the mycology of the fungi causing tinea barbae, the reader should consult Chapter 88.

The *trichophytin reaction* is usually strongly positive in tinea barbae. Mild reactions indicate infection with *T purpureum* or *T violaceum*

Wood's light. *T mentagrophytes* and *T rubrum* do not cause fluorescence in Wood's light, in contrast to *T violaceum* which invades the hair shaft and which does fluoresce.

### DIAGNOSIS

Tinea barbae should be distinguished from furunculosis, bromoderma, tertiary syphilis and lepromatous leprosy. Furunculosis is most painful and produces an inflammatory oedema. The other conditions can be readily differentiated from tinea barbae. Examination of the hair from a mycotic follicle or nodule will reveal the causative fungus.

### THERAPY

In the sycosis type, wet dressings or hot fomentations will have a soothing effect. The hair of the diseased follicles are easily extracted, to promote spontaneous recovery. Fungicides may be applied, as well as trichophytin therapy, the latter by intracutaneous injections of increasing dosages starting with 1/100.

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CHAPTER 67

# ONYCHOMYCOSIS AND ONYCHOMYCOTIZATION

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The current conception of onychomycosis, broadly speaking is "the finding of fungous elements on, or in, superficial scrapings of the nails, regardless of whether these elements have actually caused the condition, or have merely supervened on an already diseased nail". Usually the former situation is then assumed without further proof. Nevertheless, the mere presence of a micro-organism—even if pathogenic—does not *imply* that it is the causative germ. Thus, we know that pathogenic cocci may complicate scabies and eczema a process termed impetiginization, which then proceeds to show its own clinical aspect which, in its turn, may mask the primary disease. We find a somewhat similar situation in the case of moniliasis which is still considered as being most often, a secondary candida infection of a previous, non-fungal, disease. This masking of the real syndrome by supervening fungi is also known to happen in the case of pinta[1]

There are reasons for the fact that onychomycosis has puzzled investigators. In persons with fungous affections, onychomycoses are found no more frequently than in people without fungous affections. Persons with onychomycosis are very often *without any symptoms of cutaneous fungous* infection, not even, in some cases, onychomycosis of the neighbouring nails, whereas it is precisely these patients who have every opportunity to infect themselves by way of their clothes, socks, etc., or by scratching Moreover no onychomycosis has ever been found to be due to any of the fungi which might cause deep tissue changes. There is accordingly a missing link in the problem of onychomycosis, and this is not supplied by the fact that the nails may become involved in cases of tinea of the scalp for in deep tinea

[1] The presence of secondary in aders has obscured the true aetiology of pinta Indeed, not many years ago it was generally taken to be established fact that pinta was fungous disease

barbae, when the patient abounds in fungous elements, the nails are rarely affected. On the other hand, thousands of people carry fungous elements on their normal-looking nails, without showing any onychosis.

From the most important investigations in the field of onychomycosis published during the last few years (SAGHER, STÜHMER, BENEDEK, GÖTZ), we may draw the following conclusions. SAGHER proved histologically that fungi may occur in the nails. He found mycelia and spores, in small numbers, *in* the nails, and an abundance of them in the scrapings of the nail-plate. STÜHMER found fungous elements in nails of which the nail-plate was sterile! Evidently the fungus did not penetrate the nail-plate from inside to outside. To GÖTZ a micro-lesion of the underlying skin is requisite to precede onychomycosis [1]

According to BENEDEK's opinion a healthy nail cannot be penetrated by a fungus. In his view the nail must be primarily diseased before this is possible. His opinion that cheiropompholyx may involve, apart from the fingers, also the finger tips and the edges of the nails is not unreasonable, and certainly has not been definitely refuted. According to BENEDEK, the fungi *(sometimes) found in pompholyx patients are—as in the case of the* greater number of non-pompholyx patients—not the cause of the affection but a coincidence.

Even if pompholyx is a "mycid" there is no reason to reject the theory that, apart from the fingers, also the edges of the nails are involved in this "id".

It was a point of serious doubt to me whether I ought to proclaim, in this handbook, the current opinion, or on the contrary the unorthodox view. The fact that a thing is "current" does not imply that it must, ipso facto be also valid.

And in the light—or rather, in the obscurity—of the problem of onychomycosis the theory that the fungus only or chiefly invades a diseased nail should not be rejected offhand. This should be taken into account, if only to save the patient from having his nails drawn ..., and from relapses.

In the following chapter therefore, this latter opinion will be put forward, since the modern scientist can hardly be satisfied with a definition of an infection that merely covers *the presence* of fungous elements ..." etc. If this opinion should, according to the insight (and *the findings!*) of many readers incline too far to "the opposite side" then I would suggest, as a compromise, a differentiation between,

(a) true primary onychomycosis in which the fungus is the *actual causative* agent of the condition, (b) onychomycotization, where a diseased nail has been secondarily invaded by pathogenic fungi, and (c) pseudo-onychomycotization, where a diseased nail secondarily harbours non-pathogenic fungi. In analogy with impetiginization, it is not precluded that onychomycotization may also produce its own symptoms, which may even mask the primary condition. The mycotization may persist after the introductory disease or lesion has lapsed, thus requiring special treatment (see Chapter 87).

[1] See editorial post script on at the end of next chapter

CHAPTER 68

# ONYCHOMYCOSIS


TIBOR BENEDEK

Chicago


## INTRODUCTION

An attempt to present a concise survey of the "mycoses" of the nail organ is most difficult, since this subject has been flooded with utterly confused material from the dermatological and mycological standpoints since the middle of the last century

The fundamental sources of confusion are the following

1 Descriptive dermatology with its inherent tendency to create many "picture-and-label" syndromes, separated clinical forms of a disease which are aetiologically and pathogenetically identical and differ only in the severity of involvement of the nail organ.

2. The relative ease of demonstration of "microbiological flora" in the pathological decay products of the nail organ (hyphomycetes, yeast-like organisms, bacteria), both microscopically and culturally has resulted in extremely uncritical evaluation of such findings. In this way various fungi yeast like organisms and bacteria have been "assigned" as aetiological agents to different clinical forms of the same aetiological entity by various workers.

3 The lack of any scientific yardstick for the critical appraisal of the aetiological role of mycological findings similar to Koch's postulates appears very regrettable Whenever organisms have been found in decayed nail material, careful animal experiments have been performed with them to create the impression of real scientific proof of their pathogenicity Their results, however had no similarity to or any bearing on, the disease of the nail organ furthermore the

Dr Benedek has spent many years in clinical observation, mycological and bacteriological study in an endeavour to put our knowledge on an entirely new basis. His opinions although partially contrary to the common theories are most interesting S [illegible]

method of animal inoculation did not permit any inference regarding the origin and development of the human condition. (KINGERY and THIENES). The lack of familiarity with the normal saprophytic and nosoparasitic flora in the detritus of the diseased nail necessarily led to erroneous claims concerning the "mycotic etiology of the disease of the nail organ in question.

4 The workers in this field completely overlooked the fact that what they so laboriously studied was the *organism itself as such*. Whatever the result of the animal inoculation, it characterized only *this* organism's pathogenicity with reference to the animal species used. Any inference to the pathogenicity of the organism in question concerning *the human pathologic process* and its whole pathogenesis was wholly illusory

5 In addition identical clinical pictures of the nail organ are not produced by such heterogenous organisms as fungi, yeast-like organisms and bacteria. The histobiology* and histobacteriology* of the pathogen has to account fully for the essence of the whole pathological process. This thesis may be illustrated by two examples from the not so distant past. ASHFORD (1915) without taking into consideration that many yeast like organisms are constant saprophytes of the intestinal tract, made of one of them, "Monilia psilosis" the aetiological agent of sprue. The sudden overabundance of one or more species of Monilias in the intestinal tract was caused by the nutritional deficiency which altered the normal ecology of its flora. Later investigations proved that sprue is not a "mycosis" but a nutritional deficiency

A second example is the story of pinta (caraté). This was considered a "tropical mycosis" by some of the best mycologists because the *surface scrapings* revealed, both microscopically and culturally a great variety of hyphomycetes and yeast like organisms (NADCK), such as Aspergillus, Penicillium, Monilias, Monocytellas, etc. (See also tinea albigena Chapter 59)

The endeavour of this presentation shall be to demonstrate the true aetiological and pathogenetical facts behind the concept of "mycotic infection" of the nail organ. Emphasis will be laid on the pictorial documentation of the thesis.

## HISTORY

Dermatological texts of the first half of the nineteenth century (WILLAN and BATEMAN CAZENAVE, ROCHARD, SIMON MILTON, and others), made no mention of mycotic infections of the nail organ. The first author to call attention to mycosis of the nail organ was the elder MAHON while the younger MAHON gave the first description of trichophytosis and favus of the nail organ. The first monograph on onychomycosis was prepared by VIDAL (1880) and a second, more important one by PELLIZZARI (1888) The most thorough discussions on the subject are to be found in SABOURAUD'S "Les Teignes" (1910), and in the monograph of HELLER (1927) which is the most complete

* Under *histobiology* the relationship between the tissues and the pathogen, under *histobacteriology* the form cycle of the parasite in the tissues are understood.

study of the pathology of the nail organ. The publications of the last quarter of a century have added no new basic facts to our knowledge.

## DEFINITION

*Onychomycosis* in analogy to dermatomycosis, is a pathological inflammatory process of the nail matrix which is *actively and primarily* caused by the invasion of anthropophilic and/or zoophilic hyphomycetes. In the strict sense of this definition it is implicitly understood that these fungi should be *aetiologically directly responsible* for all morphological changes which the nail organ undergoes during this pathologic process. *Up to recently it was most questionable in want of irrefutable facts whether a primary (true) onychomycosis in the sense of this definition exists at all*

The existence of a "primary onychomycosis" has been taken for granted, simply in analogy with the dermatomycoses. Up to date there was no valid evidence—in fact, it has never been investigated before—whether hyphomycetes are able to invade the hard substance of the *healthy normal nail organ* as they do invade the normal hair shaft. Great credit goes to STÜTTGEN who proved the real existence of a primary onychomycosis.

## FREQUENCY

If we assume that primary onychomycosis does exist, it definitely is a rare phenomenon. ANDERSON (1872) did not record a single case of onychomycosis among 11 000 cases, which included 178 cases of trichophytosis. BULKELEY (1875) found none among 300 cases of dermatomycosis WHITE none among 180 cases of dermatomycosis. GRINDON considered onychomycosis extremely rare. SABOURAUD found only one case of onychomycosis among 500 cases of dermatomycosis *As an astute observer he noticed the rarity and sporadic* occurrence of onychomycosis and that *their direct cause remains unknown* * HELLER observed 7 or 8 cases in a huge material concerning

* "A Paris, l'onychose trichophytique est rare. J'ai pu examiner 500 cas de dermatomycoses sans rencontrer plus d'un sujet qui en fut atteint." "Le plus souvent il s'agit de cas sporadiques chez l'homme adulte et leur cause directe reste inconnue." "Tous les auteurs sont d'accord que, l'onychose trichophytique est ordinairement secondaire à une lésion préalable de l'épiderme de la main." SABOURAUD *Les Teignes* pp 452–453 Paris, Masson et Cie 1910

the diseased nail organ in the period 1896 to 1923 WIRZ did not find a single case of onychomycosis among 2311 cases of trichophytosis

HELLER, like SABOURAUD considered onychomycosis a rarity and wondered how it is possible for the nail organ, which has so much opportunity to become infected, by scratching or even just touching fungus infected areas of the skin and or scalp does not do so He emphasized that this phenomenon is one of the wholly unsolved enigmas of onychopathology "

The present author also did not observe a single case of onychomycosis among 317 consecutive cases of more or less severe dermatomycosis seen in the Marshall, Marianna and Caroline islands and on Okinawa in tropical and subtropical regions of the Pacific Ocean.

SAGHER examined scrapings of over 2000 nails from the hands and feet of 118 patients with various dermatophytoses microscopically and culturally Microscopic examination revealed mycelia in 61 patients. Excluding the yeast like fungi, growth of pathogenic fungi was noted in only 13 cases

## THE MICROBIOLOGICAL FLORA OF "ONYCHOMYCOSIS"

Among the known pathogenic fungi (1) *Trichophyton* (KITTREDGE) (2) *Microsporum* (BRESCIANI) and (3) *Achorion* (SCHOLZ and DOBEL, HELLER CANIZARES) species have mainly been regarded as the "cause of onychomycosis Among the yeast like organisms *Monilias* particularly *Candida albicans* were accused as pathogenic agents in onychomycosis (VIVARELLI, CIAROCCHI), but foremost in paronychias (FABRY HOPKINS, HOPKINS and BENHAM).

Among the *Trichophyton* species Tr acuminatum, Tr crateriforme, Tr violaceum, and Tr cerebriforme (anthropophilic) and Tr rosaceum (zoophilic) have been cultured out of the detritus masses of the diseased nail organ. From *Microsporum* species *M audouini* and among the favus fungi *Achorion schoenleini* were identified in the decaying nail material.

However beside these known pathogens a whole array of known saprophytes have been incriminated as agents of onychomycosis" in the last two to three decades (P brevicaule—WEIDMAN Scopulariopsis brevicaulis—BRUMPT and LANGERON Scopularia, Aspergillus

Mucor ramosus—SUTHERLAND-CAMPBELL Splcaria—WEIL and GAUDIN Aspergillus—BERESTON and KEIL, BERESTON and WARING)

It is of great import to underscore the fact that even the known pathogens have not been found alone in the decaying nail material investigated.

WEIDMAN found mycelia- and blastomyces-like spores in nail scrapings and isolated *nine different species* of fungi in culture. He exclaimed "Why should we single out P brevicaule from the host of others and fasten on it the burden of guilt?"

BRESCIANI found in the culture from the involved nail of the left ring finger M. audouini P candidum, Link Sterigmatocystis italica, Sacc. In the decaying nail scrapings of the right thumb of the same patient the culture yielded M audouini P digital. (Pers.) Sacc. P crustac. (Link) Tres. Sterigmatocystis italica, Sacc.

ROCKWOOD examined 44 nails "infected with fungi." The results were as follows: *Penicillium* (6 nails – 16 times), *Aspergillus* (7 nails – 50 times) *Yeasts* (3 nails – 17 times), *Epidermophyton* (1 nail – 4 times) *Scopulariopsis* (1 nail – 2 times), *Acremoniella* (1 nail – 2 times), *Penicillium sp.* (1 nail – three different species) *Torula* (1 nail – once).

On the other hand, there are also important findings which prove that even known pathogens can be present on clinically normal skin or nail organ.

CORNBLEET *investigated scrapings of clinically normal skin from hands interdigital folds of feet and genitocrural region in 100 individuals The cultures yielded known pathogens three times E inguinale (twice) M audouini (once)* WILLIAMS *and* BARTHEL, *in a series of cultures from practically asymptomatic nails in 40 cases of "tinea pedis" recovered ringworm fungi in every instance 37 nails yielded Tr interdigitale*

*Other workers like* KARRENBERG, *and* BURGESS, *did not find known pathogens on apparently normal skin Positive findings of* CORNBLEET *and of* WILLIAMS *and* BARTHEL, *however far outweigh in significance and importance the negative results reported.*

JESSNER and KLEINER demonstrated that 60 per cent. of people harbour yeast-like organisms and Candida albicans in the nail organ (nail wall, lateral grooves, and nail plate), without the existence of any pathology in any part of the nails. DESCHWANDEN strictly refused the validity of the claim for pathogenicity of Candida albicans in parony-

chias. ALEXANDER found Candida albicans as a saprophyte in 20 per cent. of all individuals with normal, healthy nail organs who were investigated.

Those who claim any aetiological role for common saprophytes like Penicillium, sp., Aspergillus sp., Mucor sp Scopulariopsis, sp etc. have based their claim on the simple fact that these hyphomycetes have been cultured from the decaying detritus masses of the diseased nail organ. The mere presence of hyphomycetes—known pathogens and known saprophytes—in the decaying material of the diseased nail is *no proof of their aetiological merits* Despite this, most fantastic claims of aetiological significance were raised for ubiquitous, saprophytic yeast like organisms, Candida albicans in particular This erroneous thesis was initiated in 1917 by FABRY

## SYMPTOMATOLOGY

Since STÜHMER's recent proof of a true, primary onychomycosis we can speak of (a) true, primary onychomycosis and (b) spurious, secondary onychomycosis" (LEWIS and HOPPER, PARDO-CASTELLO, and others) represented by the simple invasion of the decaying nail material by a host of known pathogens and saprophytes In the latter instance the soil (the decaying nail material) is prepared by another entirely different pathologic process. The true, primary onychomycosis although its existence is now definitely established is, at least for the time being an extremely rare occurrence The difference between the true, primary onychomycosis and the spurious, secondary onychomycosis" is in its clinic, aetiology and pathogenesis so great that they may not be confounded with each other in the future.

In primary onychomycosis *clinically* the most important fact is that the affected nail plates remain in their *structural aspect* completely *normal* from the posterior nail wall down to the distal free edge The surface of the whole nail plate is smooth, shiny translucent. Their curvature is perfect both in sagittal and in lateral directions. They remain translucent and pink in colour except for the portion in which the growth of the fungous elements takes place Here the nail plate reveals a strongly reflecting opaque layer of a milky white character (STÜHMER)

In STÜHMER's observations the process started in all three cases just below the posterior nail wall, in the lunular region of the nail plate. The milky-white opacity pushed forward in the nail plate with its natural rate of growth, exactly like the hair shaft is invaded by Microsporum species for instance, and the mycelium is pulled upward with the growing hair. The only inflammatory symptom was represented by a very narrow but highly red streak-like zone beautifully accentuating both the pink color of the distal normal nail plate and setting off the proximal forward moving milky white opacity.

STÜHMER was able to carry out histologic investigations in one of his three cases, making even a small wedge biopsy from the nail bed. The nail-forming rete Malpighii of the nail organ showed a distal parakeratotic cell layer. Inbetween the strata of these parakeratotic layers there were small cavities filled with eleidin. This substance appeared as a homogeneous, cell-free mass, somewhat retracted from the wall of the cavity. Eleidin was also found as free granules or clumps between the parakeratotic cells and even below in the rete Malpighi. In hematoxylin-eosin section one could observe dense strata of fungous element in the parakeratotic layer. The mycelium showed irregular septa with branching and typical arthrospore formation, almost the same picture as one sees in the hair shaft invaded by Microsporum fungi. Inflammatory reaction in the tissue was completely missing. Fungous element scould be found only in this parakeratotic layer. The rete Malpighi and the cutis revealed a completely normal aspect. Mycelia just below the surface of the nail plate moved forward with the normal rate of growth of the nail plate itself starting at the lunular region. The nail plate and the nail-forming rete Malpighi remained completely free from the pathologic process and without any inflammatory reaction.

The clinical aspect of the pathologic process looked the same whether the infecting fungus was Tr. rubeum or Achorion Schoenleini. The finer mechanism of the primary fungous infection, i.e. the entrance of the first fungous elements into the hard nail plate, remains for the time being also in the opinion of STÜHMER unknown. He assumes some kind of mechanical, thermal or chemical injury to the nail matrix before the invasion of the fungous elements can take place.

One fact stands out among the various claims for the pathogenicity of known pathogens, saprophytes, hyphomycetes and yeast like organisms in the clinical picture called "onychomycosis." This is *the identical clinical picture of the nail organ in the pathological process*.

Whether one scans the illustrations of PELLIZZARI, SABOURAUD, HELLER, or LEWIS and HOPPER, the clinical picture of "onychomycosis" looks alike, whatever organism may be suspected as aetiological and recovered from the decaying detritus of the diseased nail.

The second outstanding fact is the *diversity of the mycological findings*. By diversity is meant that *a host of different organisms* can be discovered from the same diseased nail at one time. Great investigators, such as SABOURAUD, HELLER and WEIDMAN recognized this peculiar aspect of

the aetiological problem, which unresolved, completely obscured this portion of nail pathology.

The symptomatology of the clinical picture stamped "*onychomycosis*" is simple and monotonous. However, there is one question which has never been asked from the time of the MAHONS (1820) up-to-date, even by the most eminent investigators: "*What is the primary lesion of this entity called onychomycosis?*" What anybody faces in the appearance of a "mycotic" nail does not permit even the reconstruction of the primary lesion, because it is in itself the end product of a series of pathological changes in the nail organ. In contrast, we know exactly the primary lesion of any of the tineas (trichophytic, microsporic, favic) on the glabrous skin. Similarly, we have exact knowledge of the primary lesion in tinea capitis, whatsoever the invading pathogens may be. We know exactly the natural history of a kerion celsi or sycosis parasitaria. We understand that the boggy, suppurating kerion is not the beginning of the pathologic process, but the end. A reconstruction of the primary lesion would be wholly impossible out of this.

Thirty years of intensive work on the aetiology and pathogenesis of "onychomycosis" awoke the doubt of this author regarding the existence of a true, primary onychomycosis. SABOURAUD *clearly considered even the rare instances of onychomycosis as secondary processes*. As mentioned previously, HELLER, discussing the "onychomycosis favosa" wondered how it is possible that despite the common extensiveness of the favic process on the glabrous skin and the extreme chronicity of the disease, which at times covers several decades, the infection of the nails by favus is so extremely rare, although the nails by the process of scratching and touching of favic lesions on the scalp or glabrous skin are in constant contact with the infecting agent. SCHOLZ and DÖBEL found not a single instance of involvement of the nail organ by this fungus among 71 patients affected by favus. HELLER related the experience of a Polish physician, active in the antifavus campaign, who handled yearly 2000 favus patients and did not find a single case of favus of the nail organ.

This author may refer to his experience with several hundred cases of tinea capitis, which lasted from several months not infrequently to two to four years, in which group not a single infection of the nail organ could be found.

Without a primary injury from without (as in the so-called "occupational" involvement of the nail organ in dishwashers laundry workers, fruit pickers cannery workers, etc.) or within (primary pompholyx of the nail) hyphomycetes of any description are apparently unable to invade the hard nail substance.

What appears in the dermatological and mycological literature under the term onychomycosis" is therefore most probably the chronic, usually far advanced form of *pompholyx of the nail organ* when not the secondary infection of any "occupational" involvement.



792. Onychomycosis of the nail organ caused by T. schoenleini.
*(Siemens–Leyden)*

In pompholyx the destruction of the nail plate occurs *not from without* It occurs, on the contrary *from within*, independent of the microscopical and cultural findings of whatever micro-organisms may be present externally hyphomycetes of any description or yeast-like organisms In the detritus masses of the subungual hyperkeratotic cell debris, in the laminated (scaly) layers of the nail plate, any and all kinds of organisms may find a hiding and breeding place for months or years. They vegetate there as *nonparasites* and as such they have nothing

to do with and never enter into the pathogenesis of the destructive picture of the nail organ [1]

## HISTOPATHOLOGICAL APPROACH TO THE SOLUTION OF SOME PENDING PROBLEMS

SAGHER's (1948) excellent histologic examinations of fungus infected nail plates shed some light on current problems of onychopathology and confirms some interesting data.

SAGHER examined 55 *nails* of 14 patients histologically Fifty-one nails were examined after surgical evulsion the four remaining nail plates were cut after three weeks growth, and only the parings were examined. Nine specimens taken from the *nail beds* of three patients also underwent histological examination. The *clinical description* of the nail changes in the 14 patients and the two *clinical photographs* (one showing affected fingernails the other one inolved toenails) clearly reveal that all 14 patients had a typical, chronic, mostly severe *pompholyx* of the involved nail organs. *Mycologically* two pathogens were discovered by culture (1) Tr violaceum and (2) Tr purpureum, Bang *Histological* examination of the *nail plates* revealed an entirely different distribution of fungous elements within their structure.

As to Tr violaceum, only few mycelia and spores were found on histological examination of the nail plates, in spite of the fact that masses of fungi were seen on examination of scrapings Most interestingly SAGHER underscored the fact that this distribution of Tr vio-

[1] Throughout the literature one faces the same stereotyped differential diagnostic question in view of an advanced, destructi involvement of the nail organ Is this (1) psoriasis, (2) ringworm, or (3) dystrophy due to a "general condition?" This question once raised further reasoning may go on like this. Since one or more nails are in olved, but there are no signs or symptoms of psoriasis on the scalp and or integument and since the nails are greenish or white are not stippled and are more friable and broken than occurs in psoriasis, the case cannot be psoriasis of the nail organ. Or the reasoning follows this pattern Examination for any kind of fungi is negati e thus it cannot be ringworm. What is it then? "Dystrophy" of the nail organ That the word "dystrophy" like "diathesis" is wholly meaningless and is only a comfortable escape from making a diagnosis goes without saying Others in turn, want to "differentiate" these destructive forms of the nail organ from (1) "eczema," and (2) dermatitis exfoliati a as a nail damage connected with a "systemic disorder

laceum differs from the findings of the same fungus in hair, in which the roots of the hairs are filled with spores arranged in chains, and hyphae are seldom seen. *The long mycelia in the nail plate were similar to those in the culture of Tr. violaceum.*

This latter sentence contains one of the most significant observations. It is common knowledge and a general rule of the behavior of pathogenic dermatophytes that their morphology is quite different in the parasitic stage in tissues and the saprophytic stage as in culture.



793 This type of nail involvement has also been described as (1) "chronic dermatophytosis of fingernails" – (2) "onychomycosis" or "staphylococcic paronychia and onychia" – Scrapings and filings of the decaying nails yielded a great variety of secondary nosoparasites.

SAGHER, *thus found that a typical pathogen like Tr. violaceum grew in the nail plate in its saprophytic and not in its parasitic form.* Mycelia of Tr. violaceum were seen in the uppermost layers of the nail plate.

According to the histological findings, the growth of Tr. purpureum differed entirely from that of Tr. violaceum. Tr. purpureum was found chiefly in the deepest layers of the nail plate, sometimes in its middle part, but never in the superficial layers; the mycelia appeared larger, branched and segmented; spores could not be detected with certainty in the nail plate, but were seen in masses in subungual horny substance. SAGHER emphasized with great clarity in every one of the investigated cases that (1) Tr. violaceum never could be found in the deeper (horn

zontal) layers of the nail plate, and (2) Tr purpureum, although invading the lowest (deepest horizontal) layer of the nail plate, *never invaded the Malpighian layer* In the nine specimens which were taken from the *nail beds* of three patients *no fungi* could be detected but where subungual hyperkeratoses occurred masses of spores and only occasional mycelia were found.

SAGHER s investigations are most valuable and permit definite and



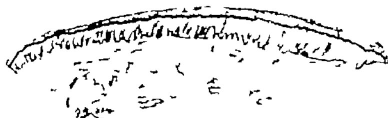
794 Section of the lateral nail wall in a case of paronychia in vesicular pompholyx of the right index finger The nail wall shows both on the upper and the lower surfaces, heavy hyperkeratotic stratum corneum and a well developed stratum granulosum. The rete Malpighi reveals a pronounced acanthosis, spongiosis and by spots, altération cavitaire. On the lower surface there is a typical intraepidermal blister filled with serum and polymorphonuclear leukocytes. Heavy inflammatory changes are present throughout the cutis. Capillaries and lymph spaces are dilated, engorged, surrounded by heavy round cell infiltration The same infiltration is present around the sweat glands The acanthotic rete Malpighi shows also infiltration by wandering cells and leukocytes. There were no organisms of any description present upon the stratum corneum or within the depth of the structure

far reaching conclusions These are (1) *even known pathogens like Tr violaceum and Tr purpureum invade only the already prepared soil* (decaying material) *resulting from* another *underlying pathologic process* (2) *they vegetate in their saprophytic morphology in the nail plate which is undergoing disintegration because of* another *basic pathological process* (3) *they never invade the only formative living portion of the nail organ the matrix and the nail bed*

## DIRECT EXAMINATION OF NAIL TISSUE

The definite conclusion was reached that whatever the microbiological flora of the chronically diseased disintegrating nail plates and the

frequently present subungual, hyperkeratotic, decaying detritus masses may be, they are secondary invaders *saprophytes* which have nothing to do with the basic pathological process which led to the



795 Section of the posterior nail wall in case of paronychia in pompholyx of the left fourth finger The section shows a heavy hyperkeratotic stratum corneum, well developed stratum granulosum, pronounced acanthosis and spongiosis with starting altération cavitaire. The cutis is only moderately infiltrated by round cells around the dilated and engorged capillaries and lymph spaces as well as around the sweat glands. The process did not reach the stage of real blister formation. The rete Malpighi is infiltrated with wandering cells and polymorphonuclear leukocytes. There were no organisms of any description upon the stratum corneum or within the depth of the structure.

changes in and final destruction of the nail organ. SAGHER s histological investigations offer further evidence for this thesis.

What one can examine in these nail involvements with far advanced



796. Detail from Fig 795 showing hyperkeratosis, acanthosis and spongiosis, and round cell infiltration of the cutaneous connecti tissue

destruction, is the *nonparasitic flora* alone. This can be done (1) microscopically and (2) culturally

For microscopic examination, *scrapings* from the subungual hyperkeratotic masses or *filings* from the nail plate can be used. The exact technique can be found in any of the numerous introductory texts on mycology. As a mounting (clearing) fluid potassium hydroxide (KOH) is still recommended by some workers. This primitive practice should finally be abandoned. It has too many disadvantages and no advantages at all.



797 Onychia in the presence of nummular eczema. (This type of involvement of the nail organ has often been regarded "acute eczema with lesions of the nails" and as chronic dermatophytosis of the hands and fingernails" because sometimes saprophytic fungous elements have been found)

The disadvantages of the use of KOH or NaOH solutions whether they are 10 or 40 per cent are 1) absorption of $CO_2$ from the air and formation of a crystalline sediment of carbonate which reduces the effective hydroxide almost to nil 2) the crystallization of the hydroxide or mostly the presence of carbonate crystals mingled with the natural fat of the hair or skin in the wet mount is most disturbing 3) if the hydroxide preparation is even gently heated, the saponification of the fat (grease) makes the observation of mycological details difficult, if not impossible 4) if such preparation is heated over the flame somewhat more energetically the structure of the hair is entirely destroyed the hair appearing like "exploded"

The advantages of chlorallactophenol formulas are the following 1) it is a cold process, no warming or heating is necessary therefore the structure of fungal elements and their natural relationship to the host cells are perfectly preserved

2) fat adherent to hairs or scales does not disturb the picture because there is no saponification 3) animal tissue (hair scale pus cells) becomes absolutely transparent leaving the vegetable elements (spores, mycelium, etc.) in clear view 4) there is no influence of $CO_2$ from the air on the solution 5) the preparation can be preserved without any further time-consuming manipulation 6) the solution can be mixed with dyes.

The following solutions are recommended as mounting fl ids by this author

✓(1) *Chlorallactophenol*

| | | |
|---|---|---|
| Rx | chloral hydrate cryst. | 20.0 |
| | acid. carbol. cryst. | 10.0 |
| | acid. lactic. pp. | 10.0 |
| S | mix and dissol on waterbath | |

(2) *Salicylated chlorallactophenol*

| | | |
|---|---|---|
| Rx | chloral hydrate cryst. | 40.0 |
| | acid. carbol. pp | 40.0 |
| | acid. lactic. pp. | 20.0 |
| | sod. salicylate | 10.0 |
| S. | mix and dissolve on waterbath | |

If staining of the specimen is desirable the *liquid of Amman* with cotton blue ($C_4B$ Poirier) can be recommended:

| | | |
|---|---|---|
| (3) Rx | acid carbol. cryst. pp. | 10.0 |
| | acid lactic. pp. | 10.0 |
| | glycerin | 20.0 |
| | aqua dest. | 10.0 |
| | cotton blue | 0.05 |
| S | mix and dissolv the first four ingredients in the order given on waterbath, then add cotton blue. | |

**DIAGNOSIS**

What is presented in the literature as onychomycosis" is the secondary fungous infection of the near final or final form of destruction of the nail organ *from within* In this stage of involvement one never can observe the primary lesion because of the thickening, discoloration and opacity of the decaying nail plate. The enormous frequency of the involvement of the fingernails, in particular is due to the fact that the nail bed as well as the nail wall carries a huge net of dense, superficial capillaries. These are constantly exposed to *thermal* (*e g* dishwasher laundress, housekeeper), *chemical* (*e g* fruit pickers, cannery workers dentists-procaine), *mechanical* (*e g* compression) injuries, thus creating points of minor resistance If that occurs, the bacterial-allergic chain reaction takes its natural course, expressed in the disturbance of the

regular production of normal, healthy nail material. The clinical diagnosis of this pathological process is *pompholyx* by definition.[1]

The course of the pompholyx of the nail organ may be acute, subacute or chronic. It may involve the matrix, the nail bed and/or the nail wall. It may appear in an isolated form, without any simultaneous involvement of the skin, or it may appear concurrently with pompholyx of the skin on hands and/or feet.

As on the palms and soles, *the primary lesion of the pompholyx of the nail organ is a deep-seated blister underneath the nail plate.* In sudden, acute or peracute cases one can observe how these blisters appear beneath the pink translucent nail plate as grayish



798 The descriptive term "onycholysis" simply means the separation of the nail plate from its bed, beginning at the free edge and progressing toward the lunula.

sharply circumscribed pinhead to millet-seed-size tiny agglomerations. Usually they contain a considerable amount of leucocytes and are, in reality, more nearly pustules than blisters.

Due to the blister or pustule formation underneath the nail plate, in progressive cases the plate will soon lose its translucency, making it impossible to observe and detect pustules in the subacute, and even less in the chronic, forms.

The pustule formation may start in the matrix (lunula); if so, the outgrowing nail plate is crippled from the beginning. Or it may start at the distal end under

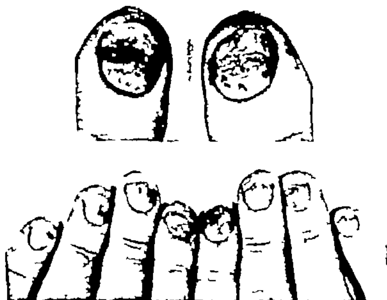
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*Editor's note.* In order to avoid misunderstanding Benedek's definition of pompholyx should be given: "pompholyx is a vesicular eruption, commencing with a primary lesion, i.e. a deep-seated, sago-grain-like blister embedded in the texture of the "normal" skin or nail bed and lacking all symptoms of an inflammatory reaction. It is further characterized by its sudden, explosive appearance, its localization to the palms of the hands and the soles of the feet, fingers and toes and to the nail organ, by its not infrequent self-limitation, by its tendency to chronicity and at times, sudden recurrences. It is not infectious or transmissable. Beside its acute vesicular form, it may reveal the subacute eczematous chronic desquamation of the palms and/or soles. The condition may erupt only underneath the nail plate or the nail wall, when called onychia and paronychia respectively.

neath the nail plate with the sequel that the distal end of the nail plate is separated from the nail bed. Detritus filling in the space between nail plate and nail bed makes the disorder even more conspicuous.

*A further sequel is the pitting of the nail plate which is caused by the pustulation and the subsequent disturbed formation of nail material.*

In further progression the nail plate shows grooves and humps, becomes crooked, loses transparency, undergoes a dirty yellow-brownish discoloration and becomes



799–800 Psoriasis of the nail organ.

scaly. This phase of the process corresponds to the "eczematous" form of pompholyx of the integument. The pustulation in the matrix may be so severe that the proper formation of nail cells is completely interfered with and the nail plate is replaced by a dirty, grayish-brown membranous material.

Pompholyx of the nail organ, which may attack only a single nail or several or all of them, is more common in connection with the simultaneous involvement of the fingers or the hands. The most severe forms can be found in [illegible], where it is usually called "psoriasis" of the nail.

Dermatological texts usually place this affliction under "onychomycosis" because one can culture all types of micro-organisms from the

keratotic detritus material. *When hyphomycetes are cultured the condition is usually called "onychomycosis" when yeast like organisms are found, it is "moniliasis" if Staphylococci are discovered it is termed "staphylococcic onychia or paronychia*

In staphylococcic onychia and paronychia there are no nail changes at all. Acute onychia and paronychia, which is caused mostly by Staphylococci, less frequently by Streptococci or Escherichia coli, is the *felon or whitlow* (panaritium) and is accompanied by excruciating pain, throbbing in the finger etc. The process may be so intensive that the nail plate is quickly undermined and the affliction can only be stopped and cured by incision and, often, by surgical removal of the nail.

In contradistinction, onychia and paronychia of the nail organ as pompholyx are subacute and mostly chronic. It is, in the worst case, tender but it never shows the heat throbbing and unbearable pain of true pyogenic infection of the nail organ.

Pompholyx is therefore in the present writer's opinion the most common affliction of the nail organ An acute attack of pompholyx of the nail organ may be self limiting but usually this is not the case. There is a tendency to extreme chronicity

DIFFERENTIAL DIAGNOSIS

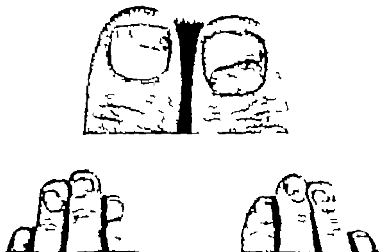
In the literature of "onychomycosis (1) psoriasis, (2) eczema" and (3) "dystrophy" are constantly considered in its differential diagnosis

(1) *Psoriasis* Some workers in the field have tried to differentiate "psoriasis" from "onychomycosis" by the discoloration of the nail plate by the inception of the process, as to whether it started at the lunular region or at the free edge whether there was much pitting and how the stipples were arranged as to whether the nail plate was buckled or there was a hyperkeratotic detritus mass under the free edge of the nail plate which was lifted up. All or any of these symptoms may or may not be present. They do not offer a basis for any differential diagnosis This condition of the nails in patients revealing a pronounced psoriasis of the skin and scalp can be called psoriasis unguium for reason of terminology

(2) *Eczema* There is a lengthy discussion on "eczema of the nail organ" in HELLER's monograph This discussion (1927) is today outdated. What is covered by HELLER under "eczema" is dysidrotic eczema, *i.e.* nothing but pompholyx. His illustrations of "eczema of the nail organ" only underscore this fact.

Since pompholyx of the nail organ may appear during the course of any other systemic disease, the systemic disease as such may not have anything to do with the pathologic process of the nail organ.

(3) *Dystrophy* Many illustrations have been published in the literature labelling severe forms of pompholyx characterized by buckling and thickening of the nail plate and accompanied by subungual hyperkeratosis as "dystrophy" The word is usually used to circumvent the lack of correct diagnosis



801-802 Onychosis in chronic cheiropompholyx.

**THERAPY**

The therapy of the true, primary onychomycosis is yet to be solved. STEINER did not discuss this problem in his publication. It will probably be mainly mechanical rather than antifungal. However due to the rarity of its occurrence, it presents only a minor problem. Quite different is the question of the treatment of the spurious, secondary onychomycosis"

According to PARDO-CASTELLO the treatment of "onychomycosis" is disappointing in many cases If the nail bed is involved, every known method of treatment may fail, opined MITCHELL. This is in general

the consensus of opinion in all the current dermatological and mycological texts. Workers in this field are beset with the idea that the condition to be treated is a "fungus" disease and they are out to kill fungi, by all means. Thus, the recommendations for this purpose are legion. Instances in which any of these recommendations may apparently work are deceptive, because the frequent *spontaneous arrest* of the nail process and following recovery look like a direct therapeutic effect.

Among the innumerable therapeutic recommendations there are *two which require some discussion* (1) *the X-ray treatment*, and (2) the surgical management.



803 Similar cases were erroneously described as "moniliasis" or "onychomycosis." Note paronychium.

(1) The X-ray treatment.—In MacKee's opinion, roentgenization is of somewhat uncertain value in this exceedingly recalcitrant affection. He states, however, that "there is not the slightest question regarding the efficiency of the X-rays in some cases on onychomycosis."

Popp and Addington (1941) recommend precautions in roentgen therapy because it is by no means a cure for psoriasis of the nails. Since the natural course of psoriasis is toward recurrence under any treatment, the beneficial effect on these complications of psoriasis, even though marked, will be at best only temporary.

*This author cannot help but repeat his advice never use X-ray irra*diation in pompholyx of the skin or in pompholyx of the nail organ. Just as it is deleterious in any type of pompholyx of the skin organ, it is deceptive and harmful for the treatment of the nail organ. In *some* cases one may see a transitory improvement, but even this is rare in

the fairly large experience of this author At least half of the patients with pompholyx of the nail organ coming to the dermatologist, beside an endless gamut of local treatment with salves, lotions, soaks, etc. have been given X ray treatment without success

Recently MITCHELL also emphasized that X ray treatment is of no value in this condition.

(2) The surgical management.—This vicious treatment is still practiced in many quarters (KILE and WELSH, EPSTEIN TAYLOR) and has even recently been recommended again (MENDHESHEIMER). The thoughtless removal (evulsion) of the nail plate and the curettage of the nail bed have their terrifying parallels in the past as useless therapeutical measures. DE BEURMANN and GOUGEROT reported that they knew of several instances in which legs and arms were amputated before the aetiological agent of sporotrichosis was discovered. The condition was confounded with tuberculotic ulcers. Those who recommend filing drilling surgical evulsion, curettage, and electrodesiccation of the diseased nail have often no sufficient knowledge of the essence of the pathologic process they are dealing with.

Any kind of manipulation on the nail plate is worthless because the crooked, buckled, pitted, scaly nail plate is *not the disease* and *not the sustaining* part of the process it is its *product* The pathological process is going on deep in the subungual connective tissue. Thus when this living but diseased portion of the nail organ is destroyed, the further pathological process is naturally stopped. But the nail never grows back again.

In 1946 the present author (see also SCHUSTER) suggested a *vaccine therapy of pompholyx of the nail organ as the aetiologically directed* management of the condition. No local treatment is given. Whatever the microbiologic flora of the diseased nail organ may be, as soon as the pathologic process is arrested and new nail plate is formed, the nosoparasitic flora loses the nutrient soil, the decaying debris of the diseased nail, and it spontaneously disappears. The only important part of the specific vaccine therapy is that period, until the *lunula is restored* When this point in the therapeutical management is reached even when further treatment stops the nail will grow out normally again [1]

[1] The situation is exactly the same as in the management of pompholyx of the palms and soles, fingers and toes. Whether the roof of the pompholyx blisters re

All that has been said refers to the pompholyx of the nail organ of the *fingers* Pompholyx, of course, may also attack the toenails Vaccine therapy of the pompholyx of the nail organ of the toes has either



804 Onychia in biologic interrelationship with nummular eczema usually called eczema of the nails.



805 Pompholyx of the nail organ in which no fungous elements could be found.

been less successful or not successful at all. The only explanation for this fact that this author can see is that the nail organs on the toes are often mechanically damaged by the shoes to such an extent that the

free from or full of nosoparasitic fungi (T interdigitale Tr rubrum or any of the many molds Penicillium, Aspergillus, Mucor Trichothecium roseum, Alternaria, Hormodendrum, etc.) no local, "antiparasitic treatment is necessary or indicated. As soon as the process is arrested the skin will peel off and the nosoparasitic fungi are automatically removed.

reproductive capacity of the matrix is not up to par. Findings of pompholyx on the toenails are mostly accidental, since patients would hardly seek help merely on this account. They are always covered, and usually crippled anyway so they are no source of social embarrassment.

There is a definite biological interrelationship between contact dermatitis and pompholyx, on one hand, and between nummular eczema and pompholyx on the other.


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## EDITORIAL POST SCRIPTUM TO CHAPTER 67 AND 68.

When the present volume was going to press Gotz Munich had just published a most interesting communication on onychomycosis reporting that fungous diseases of the skin and nails increased in Germany after the war Onychomycosis

Archiv fur Dermatol und Syphilis 195 (1953) 579–616 and subsequent personal communication
In Munich T mentagrophytes Kaufmann–Wolf (= Tr interdigitale e.g. Tr gypseum o mentagrophytes) 60 per cent. E. rubrum Castellani (Tr rubrum Castellani S bour ud) 35 per cent others 5 per cent.

he states, was most frequently seen among women (ca. 70 per cent.), but tinea of the skin more often among men (also ca. 70 per cent.). Most cases occurred between 40 and 50 years of age. Especially (and this as often in men as in women) the first toe was involved, and among women the right hand more than the left (3 : 2). As Götz too was doubtful about the infection mechanism of onychomycosis, he tried to infect nails experimentally. Neither application nor introduction of fungous material to, or into, the nails had any success, with the exception of one experiment, when the underlying epidermis was slightly eroded. From this Götz concludes that onychomycosis is impossible without a preceding micro-lesion of the skin, belonging to the nail organ. This applies equally to Epidermophyton and Trichophyton (incl. Tr. schoenleini) and less to Microsporum. Götz refers in this connection to the frequent occurrence of favus in Turkey, being rarely complicated by favus of the nails (Marchionini). He regards the following factors as requisite for the genesis of onychomycosis: (a) a fungous focus somewhere on the patient's skin (apart from some exceptions), (b) fungous elements must arrive under the nails, (c) these elements must be pathogenic, and (d) there must be a certain predisposition („Aufnahmebereitschaft") represented by a micro-lesion, which may have been caused by manicure, maceration of the skin by water, perhaps alteration of the pH and/or low temperature of the skin of the fingers and toes, pressure from shoes, etc. The thickness of the nail is unimportant with regard to the occurrence of onychomycosis, since the fungus penetrates the skin of the nail bed first. From here the hyphae penetrate the nail from underneath. Although Götz' conclusions do not fully cover those which have been put forward in Chapter 68, where cheiropompholyx of the nail organ is regarded as the most important portal of entry, he too concludes that primary onychomycosis (without a preceding skin lesion very near to the nail) does not exist.

# CHAPTER 69

# PIEDRA AND PIEDRAIA

R. D. G. PH. SIMONS
Amsterdam

## DEFINITION

Piedra is a fungous disease of the hair first described—and chiefly found—in South America and about which different views are held that have, no doubt, led to a certain amount of confusion.

On microscopic examination of the piedra nodules some observers found a resemblance to previously described cases but with a difference in the culture (MacLeod, Pereira); other opinions testify to identity of culture while stating that microscopic examination of the nodules failed to show any correspondence to those cases whose cultures therefore were identical (Kambayashi: yellow nodules; Beigel: green nodules; Behrend: nodules green and soft).

Other discoverers of cases of piedra—which they frequently considered identical with already known cases—nevertheless thought fit to give the disease another name (Behrend: Trichospora ovoides; Kambayashi: Oosporon trichospora; Morris and Cheadle: tinea nodosa).

The following names are generally used synonymously: *trichosporosis* (Vuillemin), *tinea nodosa* (Morris and Cheadle), *trichomycosis nodularis* (Juhel Renoy), *oosporon trichospora* (Kambayashi), *piedra nostras* (Unna), *piedraia* (Da Fonseca and Area Leão). All the same, these names are not quite synonymous: thus *piedraia* (Ascomycete), for one, is quite a different fungus from Vuillemin's *trichosporon beigeli* (Rabenhorst).

## EPIDEMIOLOGY

Different forms of piedra have been described in Columbia, in Brazil (MAGELHAES, HORTA, BRUMPT DA FONSECA and AREA LEAO) in Paraguay (DELAMARE and GATTI) in Argentina (ARRIAZ) in Guiana (MACLEOD AARS SIMONS) in Venezuela (BRUMPT and LANGERON) in Japan (KAMBAYASHI) in Ceylon and in India (CASTALLANI) and in Indonesia (WOLFF and GERLACH later also VERBUNT BOEDIJN and LAMPE) VAN PUTTE saw piedra in Holland—in three fair-haired boys who had come from Sumatra and the author observed a case in Holland originating from Java.

BEHREND (1890) described a case of piedra in Europe and called it *trichosporum ovoides* in 1895 UNNA reported a similar case, describing it as *piedra nostras* or *trichosporum ovale* The spores of this fungus, according to UNNA, are smaller than those of the Columbian fungus which led him to re-christen the latter *Trichosporum giganteum*

More or less similar cases were observed in Prague (WOLLSCH) Breslau (CARO), Russia (LINDEMANN), France (VUILLEMIN, DU BOIS), Italy (PAOLI) and Sardinia (LUIGI PAIS)

The affection described in 1896 by BEIGEL and FOX under the name of "*chignon disease*" was identified as piedra by BEHREND amongst others. The so-called electric wire piedra is a piedra like condition on telephone wires due to *tillandsia*

## SYMPTOMATOLOGY

Piedra is a mycosis occurring on the hair in the form of small nodules, in some cases solitary but nearly always multiple (up to 20 on a single hair).

The nodules do not invade the follicles—(the only particular on which all investigators are in agreement) and are usually dark coloured, and hard.

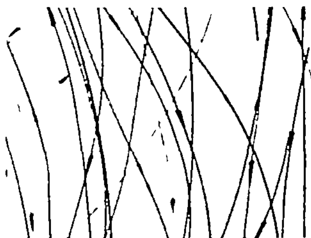
The name "*piedra*" (*cf* the French word pierre") is Spanish for stone. Early descriptions (OSORIO *et al*., CASTELLANI and HARTZELL) state that piedra is ectothrix but subsequent investigators described it as either partly or entirely endotrix, the cells of the piedra fungi penetrating the cuticle of the hair (AARS, BEIGEL, CHAVARRIA and ROTTER, etc.)

The hair is "sandy" to the touch and is said to crepitate when

combed (AARS, CASTELLANI, HARTZELL and others). According to MALCOLM MORRIS the hair smells sour. In some cases it is said that the



806. Piedra nigra.



807. Piedra nigra.

hairs stick together owing to an adhesive substance from the spores of the piedra fungi (VUILLEMIN, MACLEOD).

**AETIOLOGY**

The actual genesis of piedra is unknown.

In Columbia, Paraguay and also in Japan, piedra is found more frequently among women than among men in these parts the cause is commonly attributed to the hair-oils used by women. In Brazil and Guiana, however piedra is found predominantly in men.

AARS described the disease as occurring in young men who in Guiana, go in for much swimming (in rare cases also in non-swimmers) ARIAZ suspected a direct mode of infection when observing piedra in schoolchildren who were in the habit of wearing each others hats. A remarkable point is that this mycosis has been observed relatively often in medical men and students (Argentina, Columbia, Guiana).



808. Piedra nigra nodule.

LAMPE found the affection almost epidemically in Jakarta. Persons with straight hair (American Indians Javanese immigrants, half breeds) are said to be particularly susceptible. Among a great number of piedra patients I never saw a woman or a negro Only the hair of the head is affected. Rare cases of piedra in the axillary hair were observed in South America (AARS).

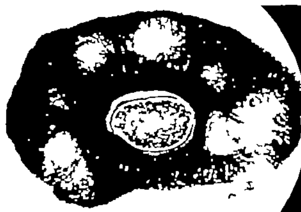
Cases observed in Europe were all localized in the beard and the moustache DU BOIS saw one case of infection of the pubic hair with piedra (*i.e.* the part moistened by urine).

CHAVARRIA and ROTTER consider the occurrence of piedra to be dependent on the humidity of the hair and for this reason hold the geographical distribution of this mycosis to be dependent upon the degree of humidity of the regions where the disease is found. This notion corresponds to AARS observations, since swimmers hair oftener gets and longer remains, wet than non-swimmers Another fact that supports this aetiology is that, in Guiana, piedra is found more often

in men than in women, swimming being far more customary in Guiana, among men than among women, the latter moreover wearing bathing-caps for the occasion. It is, further not impossible that the humidity of the hair is increased by the use of hair-oils.

LANGERON and AARS have mentioned a form of piedra in plants which they attribute to Asterinaea, and which shows a strong resemblance to the so-called Brazilian form of piedra. These fungi live epiphytically on plants.

According to LANGERON piedra is found in those parts of South



809 Piedra nigra surrounding the hair (ectothrix). Note asci as bright spots, called Horta's cysts

America where Asterineae too are found i.e. in the "Asterineae, climate" of ARNAUD with its high degree of humidity a climate therefore, in which Asterineae thrive in abundance. LAMPE states that he found piedra fungi in kali (i.e. river) water at Buitenzorg, Java. According to LANGERON the European forms of piedra are not caused by Asterineae. He discusses the fungi of Brazilian piedra together with HORTA's *cysts*" which, he states, are nothing but vermiform ascospores contained in asci.

The present writer contracted piedra of the hair of the head, in Surinam together with a number of persons with whom he used to go swimming regularly in the Saramacca canal near Paramaribo. No hair

oil or brilliantine was used in those days the hair did not stick together and neither did it smell sour

Experiments to inoculate persons or animals with piedra have always ended in failure. Smearing the pure culture into the armpits gave no result. BALLAGI stated (1926) that he succeeded in infecting rats after previous negative results with humans and with guinea pigs

## CLASSIFICATION

One of the things that have led to some confusion is the original sub-



810. Ascospores escaping from ascus in black piedra

division of piedra into a European and a non-European, or a tropical and a non-tropical form. *To classify fungi according to their geographical distribution is fact is bound to cause confusion*

Piedra was first described by OSORIO *et al* in Columbia, in 1876, as occurring endemically chiefly in the Cauca valley These authors, however regarded the nodules as being an accumulation of epithelium. DESENNE, on examining samples of piedra which they—OSORIO *et al*—had sent him was the first to assert that the disease was a mycosis

The differences between the various forms observed may be summarized as follows

(i) *the Columbian form* has also been observed outside Columbia (Brazil, PAUL RENA (1931) CHAVARRIA and ROTTER (1933) Guiana, SIMONS (1935)) while other investigators have found *the Brazilian form* also outside Brazil (Columbia, BRUMPT and LANGERON (1934) Paraguay DELAMARE and GATTI Argentina, ARIAZ Guiana, AARS)

(ii) one investigator describes piedra as being exclusively ectothrix (first findings Columbia, SIMONS) another as exclusively or predominantly endothrix (AARS, BEHOEL and others), and a third as



811 Umbilicated colony of piedra alba fourteen days old



812. Umbilicated colony becoming cerebriform. Cf trichosporon cerebriforme kambayashi.

centrally ecto- and at the extremities of the noduli, endothrix (CHAVARRIA and ROTTER (1933))

(iii) one investigator describes piedra as occurring exclusively on the hair of the head (South America) and another as found exclusively in the beard, moustache or pubic hair (UNNA, BEHREND DU BOIS, CASTELLANI)

(iv) both black and white cultures are known one investigator obtained black cultures (Brazil) another white ones (Columbia), and a third obtained both forms (CHAVARRIA and ROTTER DA FONSECA and AREA LEAO SIMONS) while finally PEREIRA (1930) published a case in southern Brazil in which the white form passed into the black thus he called *piedra sarmentoi*"

(v) many microcultural differences, moreover are known.

In the first case, therefore, it is clearly evident that there is no longer any question of a typically Columbian and a typically Brazilian form of piedra.

In the second case we are pretty safe in assuming that piedra is ectothrix. While the nodules on some freshly cut hairs appear to be firmly attached to the shaft on others they are quite clearly ectothrix.

The third case raises the question whether certain forms of "European" piedra are, actually caused by a piedra fungus, or whether they are not, in fact, cases of trichomycosis axillarum (flava and nigra), also called lepothrix the more so since BEHREND described his cases with soft nodules and light yellow cultures.



813. Cultures of black and white piedra, both one month old.

Du Bois case has remained unique ever since 1910 so that a conclusion from it would hardly be justified. CASTELLANI has described cases of piedra of the beard and moustache in India and in Ceylon.

As regards the fourth point of difference HARTZELL questions whether the various forms of piedra are not, in fact pleomorphous forms provoked by one and the same fungus. SIMONS was able to ascertain definitely from his investigation, that the black and the white forms are not caused by the same fungus. It is probable that HARTZELL's query refers to the white form only

PAUL RENA believes that the difference between the tw is based on a difference between the cultures. CHAVARRIA a

suspect the white form of being caused by contamination of the black form. BRUMPT and LANGERON are of the opinion that the synonym "piedra sarmentoi" should be dropped.

The following forms of piedra have been known up to the present

WHITE

Tr. Columbiensis discovered by OSORIO *et al.* more closely described by DESENNE, and called by JUHEL RENOY trichomycosis nodularis, and by UNNA and BEHREND Tr. giganteum, to distinguish it from the smaller forms.

Tr. ovale europiensis (UNNA 1896) or piedra nostras
Tr. ovoides europ. (BEHREND)
Oosporon trichospora japonicum (KAMBAYASHI)
Tr. beigeli europ. (RABENHORST and VUILLEMIN)
Tr. toxi (CASTELLANI)
Tr. krusi (CASTELLANI)
Tr. glycophile (DU BOIS)
Tr. equinum (FAMBACH)
Piedra alba (SIMONS)

BLACK

Tr. hortai braziliensis (BRUMPT), or Piedraia (DA FONSECA and AREA LEAO)

| | |
|---|---|
| Tr. venezueliensis (BRUMPT and LANGERON)<br>Piedra javaniensis (VERBUNT and BOEDIJN)<br>Piedra sarmentoi (PEREIRA) (black and white) | identical with piedraia |

All the above forms were described several decades ago. It would be well indeed, if the investigators once more studied their cases a little more closely with the aid of more recent results. It is quite certain that errors were made, a glaring one is that of TANIGUCHI who in 1924 observed a case of alopecia areata at a girls school, reminiscent of piedra, and which was cured by means of piedra ointments (!)

SIMONS, in an attempt at re-classification, found the form called piedraia to be the most constant.

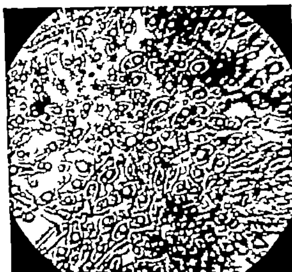
As already reported previously by BRUMPT, DA FONSECA and AREA LEAO, and also observed by AARS, section of a large number of nodules

showed up the asci quite clearly as bright spots. They correspond perfectly to the so-called *Horta's cysts*"

In some of the nodules no asci were found.



814 Septated mycelium from microculture of piedra nigra.



815. Blastospores in young microculture of piedra alba.

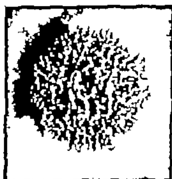
**MYCOLOGY**

As regards the microscopy of the nodules it plainly shows the mosaic structure observed also by amongst others, AARS. On examination of a nodule in potassium hydroxide under the microscope banana shaped spores may be seen to escape, after some time, at the edge they very probably spring from the asci referred to above.

Implantation of nodules on SABOURAUD's medium may often result in white cultures, i.e. in those cases where the hair has not previously been washed. When the nodule is washed up to 3 min in 70 per cent. alcohol one gets a black culture. White piedra, therefore, occurs when the hair is not washed, black piedra, when it is or has been. White cultures are caused by a white piedra fungus.

From old hairs (1 year old) it is not so easy to obtain white cultures even when unwashed they may produce black cultures. White piedra therefore, most probably behaves as what we are accustomed to call a contaminant of the black one. CHAVARRIA and ROTTER and also AARS inclined to this view.

*In that case, therefore, black piedra would be the genuine piedra, in other*



816. Culture of white piedra guyanensis.

*words, piedraia piedra, and white piedra would be "spurious", i.e. piedraia*

With regard to the culture it has been observed that the white cultures may, under certain circumstances, grow quite smooth and even, instead of cerebriform (SIMONS).

The even culture resembles in many respects that of MACLEOD's Trichosporon nodosum. When the even cultures are allowed to grow they may, after a few months, pass into the cerebriform types again; on repeated implantation they retain the latter character. The colonies moreover often grow differently in different media.

Gelatine is liquified by white piedra, on an average after 18 days, not by black piedra. White piedra, as a rule, grows far more rapidly than the black form. (CHAVARRIA and ROTTER, for this reason, believe

that it is possible for the white form to overgrow the black form by excessive growth.) Black piedra, in fact, grows exceedingly slowly its colour is black its centre, which rises like the top of a tiny pyramid appears to be sprayed with a kind of brown dust. This dust is easily wiped off when the whole of the "cone" is seen to be black and radially "pleated" or "wrinkled" The black culture is of a firmer consistency than the white.

No ascospores can be found in the microcultures of the black form (AARS, SIMONS) Only a large number of mycelium filaments clearly articulated by septa, are found. Each articulation of the mycelia has double contours.

The microcultures of the white piedra show a different picture according to age. In the beginning one finds "blastospores" also described by CHAVARRIA and ROTTER. A month later mycelium filaments may be seen, and in still older cultures (two months) also chlamydospores. If we compare these findings with those concerning piedra Columbiensis and Trichosporon ovoides, and with those of Tr bergeli we shall readily find considerable correspondence, at any rate as regards some of the phases.

### DIAGNOSIS

Piedra and piedraia must be distinguished from pediculosis and also from lepothrix, which occurs exclusively in the armpits and in the pubic region.

### THERAPY

Treatment consists in cutting the hair short (in man) and in regular application of a lotion consisting of a solution of salicylic acid 2, resorcinol 2, in iodine tincture 2 per cent.

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CHAPTER 70

# TRICHOMYCOSIS AXILLARUM

## (Lepothrix)

R. D. G. PH. SIMONS

Amsterdam

### DEFINITION

Trichomycosis axillarum is a myco-bacillary infection of the axillary and pubic hairs revealing yellow red or black concretions surrounding the hairs. The sweat in the affected region may also become coloured. (This, however should be distinguished from so-called chromidrosis when the patient produces coloured (blue) sweat in the absence of any affection of the hair) Synonyms are *trichomycosis palmellina* (PICK), *trichonocardiasis* and *chromotrichomycosis*

### HISTORY

The disease was first described by PRAXTON in 1869 He termed it trichomycosis axillaris CASTELLANI (1911) identified the causal organism as Nocardia tenuis (for the yellow type) regarding the red and black type to be due to the symbiosis of Nocardia tenuis and the *Micrococcus castellani* (CHALMERS and O'FARRAL) or the *Micrococcus nigrescens* (CASTELLANI), respectively In 1914 SCHOBL found a species of coryne bacterium. CRISSEY REBELL and LASKAS (1952) proposed that the causal organism be termed *Corynebacterium tenuis*

One often reads "leptothrix" This word means "slender hair" but actually implies a group of the *Schizomycetes* forming filamentous, unbranched threads which may fragment into bacillary elements. The word "lepothrix" means "scaling hair". Most probably the condition *lepothrix* is due to a *leptothrix*. Although this might not be regarded as, or might prove not to be, a fungus (see pages 1024–1025) we have left this chapter in this section for traditional reasons.

## EPIDEMIOLOGY

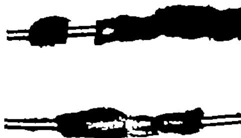
Lepothrix is most prevalent in moist climates.

## AETIOLOGY

Trichomycosis axillarum is regarded to be caused by the *Nocardia tenuis* (CASTELLANI) most probably in symbiosis with pigment-producing corynebacteria. CONANT reports that the nodules are composed of short branching mycelial elements and calls them bacillary forms of the fungus which are mixed with cocci in the black and red varieties. These bacillary forms of the fungus, however, are taken for corynebacteria by CRISSEY, REBELL and LASKAS, who have therefore suggested re-baptizing the *Nocardia tenuis Castellani*[1] as *Corynebacterium tenuis* (CRISSEY, REBELL and LASKAS).

## MICROSCOPY

By direct examination of the crushed and Gram-stained nodules bacillary and coccal elements are seen, similar to those which are found in culture. In no instance could CRISSEY *et al.* detect true branching or definite hyphal formation, although the diphtheroid type "Y" is common. On heart infusion agar CRISSEY *et al.* could grow white colonies which did not develop a mycelial down.



81. Trichomycosis axillarum or lepothrix.

## SYMPTOMATOLOGY

Trichomycosis axillarum involves only the shaft of the hairs in the axillary and pubic (rarely the beard) region. The nodules are elongated

[1] Also called *Dis[illegible] tenuis Castellani* or *Cohnistreptothrix tenuis* OTA or *Actinomyces tenuis* DODGE. Se[illegible] page 19 Vol. I

and of an irregular form. Sometimes they are hardly visible particularly the black is often overlooked in black hairs. The red and yellow varieties may stain the clothes, which is usually the only complaint of the "patient" It is said that people having trichomycosis axillarum suffer from hyperidrosis. In the opinion of the present author it is the reverse

### DIAGNOSIS

Lepothrix or trichomycosis axillarum should be distinguished from piedra and pediculosis. The discoloration should not be taken for chromidrosis, the latter being most often blue.

Since diphtheroid organisms may be found on the normal skin, it is not excluded that diphtheroid contaminants of the axillary hairs are regarded as the causal microbes of the condition. In contrast to many normal skin diphtheroids the organisms which have been isolated by CRISSEY *et al* are not stimulated in their growth by the addition of lipids and glycerin to the medium, and they ferment lactose and dextrose In addition there is a marked difference with the normal diphtheroids since they grow best at an alkaline pH.

### THERAPY

The condition is quite easily cured by shaving the hairs and/or applying a one per cent solution of tincture of iodine or formalin.

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CHAPTER 71

# INTRODUCTORY NOTES ON THE TERM "BLASTOMYCOSES"

J WALTER WILSON – Los Angeles
ORDA A. PLUNKETT – Los Angeles

As a name for a group of fungous diseases the term "blastomycoses" has been abused and misinterpreted so extensively that it probably should be discarded entirely. Many infections have been included within its scope that have little in common either pathogenetically or mycologically. The first root in the word ("blasto") should indicate that the causative organisms reproduce by the formation of "blastospores" which are the result of a definitive process called "budding". As will be pointed out later some diseases have been included whose aetiological agents do not produce blastospores. The second portion of the name ("mycoses") simply means "diseases of fungous origin" but it has been interpreted by some as indicating the production of mycelial threads by the organism. Here, again, there are discrepancies.

Mycologically the generic name *Blastomyces* has become firmly attached to only one organism *B. dermatitidis* which is the cause of North American blastomycosis or Gilchrist's disease. Indeed, whenever the term blastomycosis is used in North America without qualifying adjectives it refers to this disease. Because of mycological similarities between the two fungi the name *Blastomyces* was also bestowed by CONANT and HOWELL upon the South American fungus *B. brasiliensis* and hence the resulting disease has been called South American blastomycosis. However those workers most closely concerned with this disease do not so refer to it, but prefer other generic names for the organism such as *Paracoccidioides*, *Aleurisma* or *Lutzomyces*. To add

CHAPTER 72

# TORULOSIS, CRYPTOCOCCOSIS

## (European Blastomycosis, Buschke's disease[1])

F PIERS

Nairobi

### DEFINITION

Torulosis or cryptococcosis is a systemic and cutaneous disease caused by a yeast like fungus, *Torula histolytica* which reproduces by budding and does not produce a mycelium or ascospores

### HISTORY

The first case of this disease was described by BUSCHKE and BUSSE in 1894–95 from Greifswald, Germany. This was a case of osteomyelitis of the tibia and lymphadenitis with secondary skin lesions. BUSCHKE succeeded in isolating the Cryptococcus neoformans VUILLEMIN or Torula histolytica STODDARD and CUTLER (1946) and recognized it as a yeast like fungus Since then a limited number of cases have been reported from many parts of the world, including tropical countries. It is now known that cutaneous lesions are a comparatively rare feature (5 TOLHURST and FOX), and that involvement of the visceral organs particularly of the central nervous system, is more important, and characteristic of the disease.

[1] Note on nomenclature The writer of this article thinks that the name of his beloved teacher dermatologist ABRAHAM BUSCHKE should be commemorated in connection with the disease he discovered and to whose investigation he contributed much valuable work. Professor BUSCHKE died in Terezin in 1943, victim of Nazi persecution.

**EPIDEMIOLOGY**

Cox and Tolhurst (1946) reviewed 120 cases published until then 33 of these came from Australia.

**AETIOLOGY**

A number of strains of Torula are found as saprophytes on the skin of man and animals, on many plants, especially sugar beets, and even



818. Acneform and ulcerative torulosis.
*(Flach L. Nom-Barnes Atlas repr. Man. of clin. mycol. Saunders–Philadelphia)*

on dead vegetable material. A few strains only appear to acquire pathogenic properties.

In the human organism, Torula histolytica is found in the form of budding yeast-like cells. These are surrounded by a gelatinous capsule which gives the cells a double-contoured appearance. The protoplasma contains numerous refractile granules (but no endospores), some small vacuoles an indistinct nucleus, and in some strains a small amount of yellow brown or reddish pigment. No mycelia are seen. The organism can be cultured on the usual dextrose or beer wort media at room temperature. The growth is moist, shiny and light

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yellow or brown with a smooth glistening surface. The fungus has a slight fermenting action on dextrose. The primary growth is slow subcultures grow more rapidly

The mode of infection is unknown but it appears that the fungus invades the human organism through the skin in exceptional cases only The disease affects adults men twice as often as women.

## SYMPTOMATOLOGY

The outstanding clinical signs of typical torulosis are those of a chronic meningitis and meningo-encephalitis The onset is insidious. The temperature may remain normal throughout or more rarely present an intermittent type of low grade fever. A variety of cerebral symptoms may appear vertigo, nystagmus neuroretinitis, ophthalmoplegia, paralysis, convulsions, cerebral vomiting usually accompanied by disturbances of the reflexes. The cerebrospinal fluid is under pressure, and often has a yellow tint. There is marked lymphocytosis and the chloride content of the liquor is diminished (as in tuberculous meningitis) Torula cells may be discovered in the liquor this is not always easy since they may be mistaken for red blood cells. A positive growth can often be obtained from the spinal fluid in which the cells cannot be seen microscopically

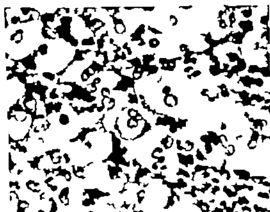
Adenopathy is a frequent manifestation of torulosis it may resemble the clinical picture of Hodgkin s disease (in a small number of cases torulosis and Hodgkin s disease were found to coincide) More rarely one finds the lungs, spleen, kidneys, the bone marrow joints and mucous membranes invaded by the organism.

## CUTANEOUS LESIONS

BUSCHKE and JOSEPH distinguish between a primary form of cutaneous torulosis which may be localized or disseminated deep or superficial, – and a secondary form in which cutaneous lesions appear as the result of metastatic spread from inner organs It is doubtful if this differentiation can be maintained, since it has been found that infection of visceral organs other than the brain may remain obscure for considerable periods. As the initial lesion of torulosis of the skin is always situated in the cutis it appears more plausible to attribute all cutaneous manifestations of the disease to metastatic spread from visceral foci.

The only exceptions occur when a glandular or otherwise super ficially situated focus breaks through towards the surface. On the other hand, cutaneous lesions are often succeeded by the development of characteristic cerebral signs.

The skin lesions of torulosis first appear as acneiform infiltrations which soon break down and form torpid, ecthyma like ulcers. These may spread, and so produce large irregular areas of ulceration with sharp slightly infiltrated and undermined margins. The secretion of



819 Torula histolytica in a subdermal abscess.
*(Fessel-San Francisco)*

the ulcers is characteristically glary and of a reddish tint. The lesions do not cause much pain. Areas of central spontaneous healing may lend a serpiginous appearance to older foci Complete involution never occurs. Smears from the ulcers show leucocytes, red cells, nuclear débris and numerous torula cells and macrophages. They can be identified by budding forms, double contours and the granular protoplasm. They should only be accepted as evidence of torulosis if they are gained from the deep layers of the granulating tissue

Foci caused by the break through of deeper-seated processes present similar features the connection with an infected gland, bone, etc., is usually obvious. The Cryptococcus neoformans may be found in the

tissues, spinal fluid and exudate as an encapsulated budding cell which may contain granules. The organism grows readily on SABOURAUD's medium forming a creamy colony The colour varies from cream to brown or orange The Cryptococcus neoformans is pathogenic for all laboratory animals



820 Histology of torulosis.
*(Paul-San Francisco)*

## PATHOLOGY

The epidermis shows considerable intercellular oedema and irregular proliferation. It is often pervaded by polynuclear leucocytes. Torula cells may be found enclosed in cells of the rete Malpighi Parakeratosis of the horny layer is not rare. The corium shows a heavy granulomatous infiltration with histiocytes endothelial cells, macrophages and giant cells—all of which may contain torula cells. This granuloma has little stability and areas of necrosis are frequent within it. These show complete destruction of the original cutaneous tissue (including the elastica) which is replaced by an irregular mass of leucocytes, fibrine red blood cells cellular detritus and torula cells. A caseating type has been described in a few cases while in others the granuloma was of a myxomatous character and in still others was it completely uncharacteristic. Areas of fibrosis occur in cases where spontaneous healing has taken place

### DIAGNOSIS

In order to exclude the cutaneous manifestations of other granuloma forming organisms and of tuberculosis and syphilis a determined attempt should be made to demonstrate torula cells from the pus of the skin lesions, or to grow the fungus from pus or cerebro-spinal fluid. Animal inoculation is usually successful in mice and rats, less so in guinea pigs and rabbits. The disease appears in animals as a pseudo-tuberculosis or as a septicaemia with abscess formation. The assistance of a neurologist will be required to exclude a tumour of the brain, meningitis and neurosyphilis if the disease is limited to the central nervous system.

### PROGNOSIS

The tendency to spontaneous healing seen in some cases of cutaneous torulosis is deceptive. No complete spontaneous cure has ever been reported and, as mentioned above, the cutaneous lesions are to be regarded as precursors of visceral lesions. Involvement of the central nervous system always ends fatally and torulosis of other inner organs has a very poor prognosis.

### THERAPY

In all systemic mycoses large doses of inorganic Iodine (Pot. Iod., Lugol's solution) should be given for long periods, at the risk of intolerance. Some symptomatic improvement usually results—which at present is all we can do for the unfortunate victims of torulosis Repeated lumbal puncture gives some relief in cerebral cases Chemotherapy and antibiotics have proved ineffective so far

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CHAPTER 73

# NORTH AMERICAN BLASTOMYCOSIS

## (Gilchrist's disease)

PAUL FASAL

San Francisco

### DEFINITION

North American Blastomycosis or Gilchrist's disease is a chronic infection caused by *Blastomyces dermatitidis* also classified as *Zymonema dermatitidis*. It is characterized by granulomatous and suppurative lesions and occurs in a primary cutaneous and a systemic form. The causative organism shows a special affinity to skin, lungs and bones.

### HISTORY

In 1894 GILCHRIST found double contured round organisms in a section of a verrucous lesion from the dorsum of the hand, diagnosed by DUHRING clinically as scrophuloderma. Later GILCHRIST and GILCHRIST and STOKES were able to find the same organisms which they named Blastomyces dermatitidis in other cases and to isolate them by culture.

### EPIDEMIOLOGY

North American Blastomycosis is for all practical purposes limited to North America, with only isolated confirmed cases having been described in Canada, England and France. It was originally called Chicago's disease but has since been observed in at least 28 states. Most cases reported from Europe, Central and South America, and Asia do not show enough laboratory evidence to make diagnosis certain.

**AETIOLOGY**

Blastomyces dermatitidis has been found in plants and animals. Damp rotting wood seems to be its favorite location. Infection from man to man is very rare. A physician who injured his finger while performing an autopsy on a case of systemic blastomycosis developed cutaneous blastomycosis proven by culture and biopsy at the site of injury (EVANS.)

Most infections, however, seem to occur from contact with plants or



821. North American Blastomycosis. See also page 53 Vol. I
*(Goldman–Cincinnati–Ohio)*

animals. Trauma is a predisposing factor. In the systemic form the most frequent way of entry is inhalation, while in the primary cutaneous form the infection occurs through the skin. *The incubation period ranges from one to three weeks.*

While most of the patients suffering from North American Blastomycosis are farmers or people who handle animals and plants in some occupational way, there are numerous cases in which the patient's occupation does not give a clue to the source of the infection. Males

are about nine times as frequently affected as females The age range is from eight months to 73 years.

Blastomyces dermatitidis is a yeast like budding fungus Direct examination of pus dissolved in a 20 % solution of potassium hydroxide reveals budding organisms 7 to 20 micra in diameter with thick walls which by their high refractility create the impression of a double contour Culture on blood agar incubated at 37° produces small compact waxy colonies, which on microscopic examination show budding cells. Culture on Sabouraud agar gives white filamentous growth and on culture mount mycelia with chlamydospores are seen. Animal inoculation is successful in mice, less so in rats, and not at all in rabbits and guinea pigs which is important in the differential diagnosis, for instance with Coccidioides immitis Cultures should be kept for three weeks, although growth usually occurs sooner

## PATHOLOGY

In primary cutaneous blastomycosis the surface of the epidermis is irregular often consisting of hyperplastic horny masses or layers of dried serum polymorphonuclear leukocytes, and cellular detritus. The most striking features occur in the rete Malpighi. The rete pegs are broad and extend deeply and irregularly into the corium, where they frequently anastomose and ramify The acanthosis is often so excessive that the picture of pseudo-epitheliomatous hyperplasia is present and the diagnosis of squamous cell carcinoma may be considered or even erroneously made. This can happen especially in oblique sections where islands of epithelial cells may appear to be deep in the cutis especially if these present numerous mitoses and even pearl formation.

Important findings are numerous large abscesses, intra and also sub-epidermal filled mainly with polymorphonuclear leukocytes but also showing some red blood cells, giant cells and the causative organisms

In the corium there is an inflammatory infiltrate often assuming granulomatous features, consisting of lymphocytes, plasma cells, epithelioid cells polymorphonuclear leukocytes and giant cells True tubercles do not occur but occasionally a tuberculoid structure is suggested. The giant cells are mostly of the Langhans type but occur

not only in connection with the infiltrate but also entirely independently of it and especially of its epithelioid cells. In addition to the organisms they may contain vacuoles The number of eosinophiles in the infiltrate varies considerably and is of no diagnostic significance. The infiltrate can invade the appendages and can reach considerable depth.

Blastomyces dermatitidis, seen in tissue sections as a round or oval organism with a thick refractile wall, multiplies by a single bud The



822. North American blastomycosis.
*(Dermat Dept Univ Calif )*

newly formed cell separates from the mother cell only after it reaches about half of the latter's size. Therefore one finds organisms often in pairs of unequal size attached to each other

The protoplasm of Blastomyces dermatitidis is granular and sometimes shows vacuolization. The organisms can be found within the giant cells between epithelial cells, freely in the abscesses and in the infiltrate.

While Blastomyces dermatitidis is occasionally seen in such large

numbers that the diagnosis does not present any difficulty this is not always the case. Often there are only very few organisms present and



823 North American blastomycosis of the ear
*([illegible])*



824 North American blastomycosis
*(Dermat Dept Univ Calif)*

several sections have to be examined thoroughly in order to find them. In such cases differential diagnostic problems occur

In the systemic form pulmonary lesions show coagulative necrosis in the center imitating caseation necrosis of tuberculosis. Cavities can be present, but are usually not as large as in tuberculosis. Grossly the picture can be that of a confluent bronchopneumonia or a miliary dissemination.

The pyemic abscesses of the skin seen in the systemic form, show numerous organisms in their walls, either free or within giant cells, in an otherwise uncharacteristic granulomatous infiltrate.

## SYMPTOMATOLOGY

Since primary cutaneous blastomycosis is caused by exogenous inoculation it is most often located on exposed surfaces of the body like



825. North American blastomycosis.
*(Walter Wilson—Los Angeles Calif.)*

the face, wrists, hands (dorsa) and legs. However any other part of the body surface can be affected; a relatively frequent site is the external genitalia. As a rule it is not found on scalp, palms and soles.

The primary lesion is a *papule* or *pustule*, rarely a vesicle, which enlarges slowly and becomes crusted. If the infection takes place in

an injury the original traumatic lesion does not heal and eventually becomes the site of the primary papule.

In the course of several months a plaque measuring several centimeters forms. This plaque presents a papillomatous wartlike surface. Sometimes it is completely or partially covered by crusts. Underneath ulceration can develop

*The most characteristic feature of the lesion is its border* which rises steeply from the normal skin. In it there are numerous abscesses most



826 North American blastomycosis of the tongue.
*(Orw G Castle-Bela Herbmuth)*

of them minute, but some visible to the naked eye The surface of the border is usually intact.

Healing takes place from the center which becomes depressed. The papillary formations flatten and the secretion decreases The border appears more prominent and elevated. A scar forms, which in the beginning is thick and leathery but in time becomes thin and atrophic. Due to contractures the scars can lead to great disfigurement and functional impairment, especially when located around eyes or lips

*The primary cutaneous lesion* is single and affects only a circumscribed area. However additional plaques may form, often in close proximity

and occasionally large areas can be affected, like a whole extremity These plaques are crusted, moist, verrucous and show a serpiginous configuration.

*The mucous membranes* are as a rule not affected in North American blastomycosis, an important feature in the differential diagnosis with South American blastomycosis occasionally lesions occurring on the border of skin and mucosa, for instance on the lips can lead to invasion of the mucous membranes In the course of the disease these cutaneous lesions may show spontaneous remissions, exacerbations and relapses over many years. The scar tissue often



827 North American blastomycosis resembling granuloma venereum.
*(Orr G Costa-Bele Herr-ots)*

harbours an active focus. The lesions are painful on pressure, especially when ulcerated. One of the most unpleasant features is the odour The general health in primary cutaneous blastomycosis is remarkably undisturbed. There is occasional fever Lymphadenitis is as a rule not present.

The most serious complication which can arise from primary cutaneous blastomycosis is generalization of the disease and development into the dangerous systemic form.

However origin of systemic blastomycosis from a primary cutaneous blastomycosis is not as common as pulmonary infection

acquired by inhalation. *The early symptoms of pulmonary blastomycosis* are often vague cough, and chest pain occur frequently accompanied by fever and loss of weight. Later the disease can imitate pulmonary tuberculosis so completely that the diagnosis is made only at autopsy From the lungs the lesions are distributed to the subcutaneous tissues, bones, joints, internal organs and central nervous system. The *bones* most often affected are the vertebrae. Of *internal organs* besides the lungs, kidneys heart and prostate are frequently involved

As the skin lesions of the systemic form are caused by haematogenous spread, their distribution is symmetrical they are found mainly on the



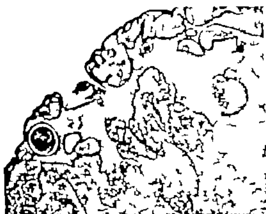
828. Blastomyces dermatitidis in the epidermis.

trunk. The fundamental lesion is a subcutaneous abscess resulting from a generalized pyaemia. The clinical appearance can suggest cold abscesses or furunculoid lesions. When these deep abscesses break through, ulceration can occur

*The prognosis* of primary cutaneous North American blastomycosis is good, as far as life is concerned. Relapses can occur Areas which clinically look healed can be the source of fresh manifestations. Scar formation in areas like the face or over joints may lead to disfigurement and contractures Primary cutaneous blastomycosis can become the origin of a systemic infection and thereby be of serious consequence

The prognosis of the systemic form is poor It has a mortality of

70–92 %. A combination of the results of the intradermal vaccine test and the complement fixation gives valuable information regarding the prognosis, especially in the systemic type, according to D. T. SMITH. Positive intradermal test with negative complement fixation has a good prognosis, while negative intradermal test with positive complement fixation is prognostically bad.



829 North American blastomycosis: acanthosis, intra- and subepidermal abscesses. Inflammatory infiltrate in the cutis.

#### THERAPY

There is no specific therapy against North American blastomycosis. *Penicillin* and some of the *sulfonamides* occasionally seem to influence the disease beneficially, due only to their action against secondary invaders; they are not specific against Blastomyces dermatitidis and neither are streptomycin, aureomycin, and chloromycetin.

In primary cutaneous blastomycosis *surgical excision* or removal by curettement followed by electrodesiccation or freezing with carbon dioxide snow is recommended in early localized cases. When more advanced X-ray therapy is often helpful.

*Iodides* have been used for many years in the treatment of North American blastomycosis and good results have often been observed, when high doses are employed. They are given as sodium iodide intravenously or potassium iodide by mouth. In vitro iodides are in-

effective against Blastomyces dermatitidis Their action in blastomycosis is apparently directed against the granulomatous tissue, similar to that in syphilis and tuberculosis

Iodides have to be given with care they can be most harmful if administered to patients showing marked allergy to the infecting



830 North American blastomycosis giant cells in the epidermis and cutis.

fungus In such cases desensitization with a vaccine is advisable before instituting iodine medication. Routine intradermal testing should be done in every patient before iodine therapy is begun.

*Neo-arsphenamine* may be helpful, especially when a patient does not show any further progress on iodides Intramuscular injections of colloidal copper have been reported beneficial.

*Vaccine therapy* is a controversial subject In addition to its use in desensitizing hypersensitive patients before starting iodides, vaccine is also employed therapeutically and good results are claimed by some authors

Lately there have been reports of successful treatment of North American blastomycosis with stilbene derivatives (diethylbestrol, stillamidine)

In the systemic form high doses of iodides are the accepted therapy at present.

**DIAGNOSIS**

The clinical diagnosis in a typical case does not present great difficulties. Conditions which should be considered in the differential diagnosis are

*Deep mycoses* caused by other organisms, especially chromoblastomycosis and the verrucous form of sporotrichosis tuberculosis verrucosa cutis bromoderma and iododerma gumma mycosis fungoides pemphigus vegetans granuloma inguinale.

It is essential to confirm the clinical diagnosis by laboratory methods

The causative fungus can be demonstrated in smears, by culture and animal inoculation. The best place to obtain material is the small abscesses in the border of the plaques. If one examines fresh pus under a coverslip and does not find budding LEWIS suggests to ring the preparation and to re-examine it after a few hours. Histopathological examination is also well suited to establish the diagnosis.

A useful adjunct but not as certain as the just mentioned methods is the intradermal test with a heat killed vaccine or a culture filtrate. 0 1 ml. of a dilution of 1 1000 of Blastomycin or Blastomycetin is injected intradermally the reaction is of the delayed tuberculin type. It suggests a previous or present infection with Blastomyces dermatitidis, but occasionally cross-reactions with coccidioidin, histoplasmin and, rarely with sporotrichin are observed A negative reaction unfortunately does not rule out infection.

The complement fixation test with an antigen prepared from growth of Blastomyces dermatitidis on blood agar is usually negative in the primary cutaneous form.

*Tuberculosis verrucosa cutis* and *lupus vulgaris verrucosus* can present similar epidermal changes with papillomatosis and even some abscess formation. However in lupus vulgaris true tubercles are found in the corium and in tuberculosis verrucosa cutis caseation is present and the number of giant cells is not as great as in GILCHRIST's disease

*Bromoderma* and *iododerma* show similar epidermal changes but the suppurative features are more pronounced. The abscesses consist mainly of polymorphonuclear leukocytes which also predominate in the infiltrate in the corium. As a rule there will be no giant cells. In pemphigus vegetans and vegetant pyoderma, which also have to be

considered in the differential diagnosis, the abscesses contain mainly eosinophiles *Chromoblastomycosis* gives a histopathological picture identical with North American blastomycosis but the organisms are characterized by their deep brown colour spherical form and the fact that they reproduce by splitting and not by budding *Framboesiform syphilis* and *yaws* give similar epithelial changes with massive acanthosis, papillomatosis, abscesses, and even an occasional giant cell in the infiltrate, but the perivascular arrangement of the infiltrate, the predominance of plasma cells, and the vascular changes make the correct diagnosis possible.

*European blastomycosis South American blastomycosis* and *coccidioidomycosis* present occasionally a similar picture. However Torula histolytica, although a budding fungus is not double contoured and is smaller than Blastomyces dermatitidis In *paracoccidioides brasiliensis* multiple budding is observed, showing a ring of small dots, and Coccidioides immitis is characterized by endospores which never occur in Blastomyces dermatitidis.

The *pseudoepitheliomatous hyperplasia* can be differentiated from squamous cell cancer by the intact basal cell layer Furthermore, the individual squamous cells in the deep epithelial islands are well differentiated and do not show individual cell keratinization. The inflammatory infiltrate in the corium and especially in the epidermis is more marked than in squamous cell cancer

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# SOUTH AMERICAN BLASTOMYCOSIS

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Rio de Janeiro

## DEFINITION

South American blastomycosis is a chronic disease of the skin, mucous membranes, lymph nodes and viscera, caused by a yeast-like fungus, which multiplies by simple or multiple budding and exogenous sporulation in the tissues and which produces hyphae and conidia in cultures at room temperature. Principal synonyms *Brazilian blastomycosis Lutz Splendore-Almeida disease Paracoccidioidal granuloma Paracoccidioidomycosis*

## HISTORY

In spite of its considerable morphological differences, which had already been noted by LUTZ (1908) who was the first to describe the fungus, the causative organism of this mycosis was identified as *Coccidioides immitis* SPLENDORE (1909), who also found the fungus to be different called it *Zymonema brasiliensis* and VIANNA gave a very clear description of these differences (1913). Years afterwards, HABERFELD (1919) gave a new name to the fungus—*Zymonema histosporocellularis* In 1930 ALMEIDA verifying and classifying the differences observed by the first three authors, described the new genus *Paracoccidioides* while preserving the specific name *brasiliensis* On the whole this classification was favourably received, the family *Paracoccidioidaceae* CIFERRI and REDAELLI having even been created. In 1939 however FONSECA regarded the credentials of *P brasiliensis* as a species as doubtful. He described a new generic name —*Lutziomyces* maintaining the specific

name *histosporocellularis* In 1941 CONANT and HOWELL, in view of the similarities between this fungus and the causative organism of North American blastomycosis (*Blastomyces dermatitidis*) included the two parasites in the same genus, calling the fungus which causes the Lutz disease *Blastomyces brasiliensis* At different times other terms were applied to this fungus but it is most frequently referred to as *Paracoccidioides brasiliensis* Two species subsequently created within this genus by ALMEIDA and MOORE— cerebriformes" and tenuis —come under the synonym of *P brasiliensis*

## EPIDEMIOLOGY

Outside Brazil, where there is a high incidence of this mycosis, it also occurs in other South American countries, such as Argentina, Uruguay Paraguay Peru, Bolivia Ecuador Venezuela and Colombia. It also occurs in Central American countries such as Costa Rica. In Brazil its incidence is highest in the states of S Paulo, Minas Gerais and Rio de Janeiro but it is also encountered in nearly all the other states of the union, including the Amazon region.

The disease mainly occurs in suburban or rural districts. It preferably affects individuals whose activities facilitate a close contact with plants such as farmers charcoal burners hunters, etc. Cases occurring right in the city have however been reported in individuals who have never left the town. The mycosis mainly occurs in adults from 20 to 30 years of age its incidence in men being 10 times as high as that in women.

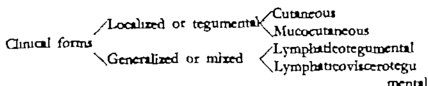
In some cases the initial lesion, which usually appears in the mouth or its immediate vicinity is apparently due to the habit, which is widespread in the interior of the country of bringing plants to the mouth to chew them or particularly to pick the teeth. In the lower limbs the initial lesions are due to injuries sustained in the field, which gaps in the continuity of the skin act as portals of entry" Primary visceral forms are caused by direct penetration through the alimentary canal (abdominal forms) or the respiratory tract (pulmonary forms) of contaminated material or dust particles containing fungi

## AETIOLOGY

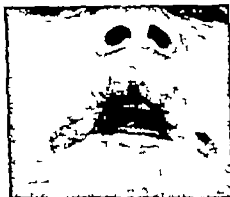
LUTZ disease is caused by a yeast like fungus termed *paracoccidioides brasiliensis* (ALMEIDA) which is described in the section mycology of this chapter

## SYMPTOMATOLOGY

It is very difficult to separate the "clinical forms" as they all overlap and usually represent various stages of a single progressive disease. In order to facilitate their study to a certain extent they may, however, be subdivided as follows:




The "*localized cutaneous forms*" run a slow course and are late in in-



831. South American blastomycosis. Mixed form. Muco-cutaneous lesions with lymph nodes and lungs involvement. Cured with sulphonamide therapy

volving the viscera. This depends upon the extent to which the orotomial "*mucocutaneous forms*" rapidly invade the lymph nodes and interior organs, particularly the lungs. Simple cutaneous forms are exceptional, but there is definite evidence of their occurrence. They are localized in the vicinity of or far from the oral cavity, in which case they may appear in the trunk or limbs. Mucocutaneous forms are the most frequent.

The existence of simple, primary *visceral forms* has not yet been established sufficiently, nor has that of the forms claimed to involve the lung or intestine. As far as the few cases reported in the literature

are concerned, it is most likely that the initial lesions of the skin passed unnoticed.

In the more common forms of the disease the *initial lesion* appears to occur somewhere in the gums, subsequently spreading to the cheeks, the velum palatinum and the tongue. From the lips and especially from the commissures of the lips, the ulcer proceeds to invade the skin to a greater or lesser extent. A similar process may occur in the skin of the borders of the nose, although nasal lesions are less frequent. In the oral mucosa the lesions may be limited to the anterior vestibular region or they may spread to the posterior region, involving the



832 South American blastomycosis. Lymphaticotegumental form with swollen lymph nodes under the maxillae and the tongue

trachea and the pharynx, in which case they are far more severe resulting in destruction of the glottis and epiglottis. These oral lesions consist of smooth ulcers, dotted with punctate haemorrhages and considerably infiltrated, the cheeks and lips becoming hard and firm. Neither the mouth nor the nose shows the mutilating destruction of tissues so frequently observed in leishmaniasis. This is an important feature in differential diagnosis. The lesions are not painful in themselves, but swallowing is difficult and causes violent pains. Therefore the patients feed poorly and soon develop a state of cachexia. The

disease is also marked by an uncontrollable sialorrhoea, so that deglu tition, which is dependent on saliva, disappears as protection.

Very soon *the lymph nodes* of the adjoining tissues are involved and they may be found to be enlarged in the neck, above the clavicle and under the maxilla and tongue. Frequently they rapidly become soft and fistulized, secreting a creamy pus, in which the fungi multiply rapidly A similar process occurs in the internal lymph nodes, especially in the hilus pulmonis and mesentery where they occasionally become indurated, giving rise to tumorous structures palpable through the



833. South American blastomycosis simulating pulmonary tuberculosis.

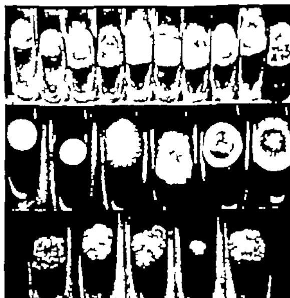
abdominal wall. The superficial tissues of the skin particularly those of the thorax, are also affected, the softened lymph nodes rupturing and giving rise to "cold" ulcers.

*The lung* is affected relatively early and the latest national and foreign statistical data regarding pulmonary involvement in South American blastomycosis agree in claiming it to occur in over 80 per cent. of the cases. Clinically cases may be observed which cannot be differentiated from pulmonary tuberculosis and even by X-ray a differential diagnosis is often difficult. Fungi may be isolated from the sputum, whether

haemoptysic or not. The disease is characterized by a constant cough and irregular rises in temperature

*The intestinal lesions* also resemble those of tuberculosis They are localized in the large intestine, particularly in the caecum, and give rise to diarrhoeal and haemorrhagic manifestations.

*The spleen and liver* are frequently involved and found to be enlarged. This is followed by involvement of the kidneys, pancreas, adrenals, gonads myocardium and nervous system. The haematogenous dissem



834 Cultures of *Paracoccidioides brasiliensis* (*Lutziomyces histosporocellularis*) Smooth cerebriform colonies After Leão & Cury *1950*

ination of the fungus may also result in the appearance of metastatic lesions of the skin, which may occasionally occur in considerable numbers.

## MYCOLOGY

*a*) *In the tissues the fungi appear as round cells* with a capsule showing a double outline and varying in size, measuring from 3—6 μ to 20—40 μ in diameter They multiply by simple or multiple budding into 3 to 5

elements, and less frequently by exogenous sporulation (= cryptosporulation) As a rule this is observed in the interior of giant cells. In this process a part is possibly played by particular cells, although they apparently have the same form as the budding cells In exogenous sporulation the chromatin divides into blocks, which are arranged at the periphery near the capsule, into which they finally penetrate through the openings which it contains, now becoming organized on the outside in the form of small spores of 1 to 2 μ. The whole presents the well-known appearance of a "steering wheel" The capsule around these small spores is dull. Finally the mother cell is exhausted, leaving the capsule which is flattened and continues to resist the defence reactions of the tissues for a considerable period Occasionally the interior of giant cells is also seen to contain numerous minute fungus forms, presenting the appearance of "dust" Their origin has not been definitely established and they are sometimes seen to be accompanied by large fungus forms Obviously they largely contribute to the dissemination of the parasites in the organism. On the other hand the interior of certain large cells, more than 30 μ in diameter is found to contain round (metachromatic) structures, which occasionally show an aspect of endogenous sporulation.

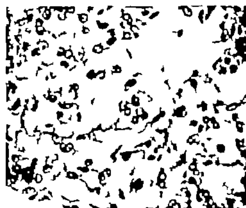
*b*) In *cultures* the fungus grows very slowly and its growth is difficult to obtain. In the incubator at 37° C, in blood agar, the fungus will produce smooth colonies composed of round and gemmating cells as in the tissues. In Sabouraud's glucose medium at room temperature, hair like, somewhat greyish colonies (showing a "rat's hair" appearance) are seen to grow in which microscopic examination will reveal a small number of sessile round or oval, conidia. Even at room temperature some specimens appear smooth and cerebriform. When mycelian cultures are grown in the incubator at 37° C, they will revert to the yeast like phase

### DIAGNOSIS

Material obtained by biopsy or curettage of lesions, pus from liquefied lymph nodes, and sputum from patients with pulmonary lesions may be examined between slide and coverglass in a physiological salt solution. This examination will reveal round, refractive cells, varying in size and showing the characteristic gemmation. The material may

also be stained in smears by Leishman's or Giemsa's method, the fungi appearing with bluish plasma and little chromatin, pink in colour As a rule the capsule does not stain. In sections treated with routine staining methods (haematein-eosin) the fungi will also appear very clearly but certain structural details, particularly those of the capsule, will be observed more clearly by silver impregnation (methods of PERDRAU or LEVADITI)

Exogenous sporulation is a highly characteristic, but inconstant, feature, which usually occurs in the interior organs and very rarely in the oronasal lesions, which provide material for examination in the



835. South American blastomycosis. Granulomatous reaction in the lung epithelioid and giant cells, with minute forms of the fungi (*P. brasiliensis*)

greater part of the cases The diagnosis should be based upon the finding of multiple budding so that, without this criterion, a diagnosis will be impossible in many clinically and histopathologically typical cases

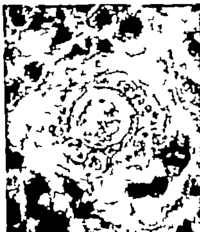
The same material used for direct examination may also be employed for inoculation in suitable culture media, to which antibiotics (penicillin, streptomycin) should be added to prevent the growth of contaminations. Response is very slow occurring only after 5 or 6 weeks in some cases In the incubator at 37° C blood agar is used and fermenting and budding forms are obtained. In Sabouraud's glucose

medium at room temperature hairy colonies will grow with mycelia which are not very long and a small number of conidia.

In addition, this material may be inoculated into sensitive animals. Therefore the hamster is the animal of choice, as the fungus will spread through its organism whatever the method of inoculation may be, even involving the nervous system, as occurs in the human form of the disease. A response is obtained within 30 days but the animals are resistant to infection for more than 6 months. For diagnostic purposes, subinoculation or inoculation in culture media, the enlarged



836 South American blastomycosis. Typical tubercular follicle with fungi (*P brasiliensis*)



837 Section of lymph node. Typical form of exogenous sporulation (accelerated multiple budding) of *P. brasiliensis* (*Lima & Gois 1950*)

testicle or the peritoneum is punctured and fungi are found in the material obtained. The hamster is particularly suitable for pathogenic or therapeutic studies.

*Intradermal tests* may be made with antigens prepared from fungus cultures ("paracoccidioidin"). 0.1 ml of antigen is injected and the results are read after 24 and 48 hours. Positive tests are characterized by oedema, erythema and local pain while some cases show severe reactions with fever and malaise. The use of the intradermal test is

limited both because it constitutes a group reaction and because its results are inconstant.

## DIAGNOSIS

Mucocutaneous forms should be differentiated from leishmaniasis, yaws, syphilis, etc. In mixed forms Hodgkin s disease, pulmonary tuberculosis, leukaemia, histoplasmosis and actinomycosis should be taken into account. Cutaneous forms should be differentiated from LOBO s disease and other related blastomycosis occurring in the Amazonic districts.

## HISTOPATHOLOGY

In *biopsy* material from the skin and mucosa a marked acanthosis and minute abscesses are observed in the epidermis while the corium shows an extensive granulomatous monohistiocytic infiltration, studded with minute abscesses and tuberculoid follicles, with giant and epithelioid cells The fungi are usually distributed in the minute abscesses and tubercles but they may also occur in small numbers being occasionally lodged in the epidermis

The fungi found in *autopsy* material in generalized forms give rise to lesions in all the principal viscera. In order of frequency of the lesions the various organs are ordered as follows lungs intestines liver spleen, kidneys, pancreas adrenals myocardium, gonads and nervous system. Only the bones are rarely affected, although fungi are fairly often found in the bone marrow Occasionally whitish nodules are observed macroscopically in the lungs, liver spleen and kidneys. In the large intestine, particularly in the caecum and appendix, ulcers, originating in Peyer s patches are found. The lymph nodes of the mesentery and peritoneal wall are enlarged. The same occurs with the lymph nodes of the hilus pulmonis. The lungs may contain numerous, irregularly distributed, palpable small nodules. In all these lesions microscopic examination of the various organs will reveal a granulomatous reaction in which the fungi with their particular characteristics are distributed In the lungs intestines spleen and liver typical tuberculoid follicles are formed, with giant and epithelioid cells. The same thing occurs in the lymph nodes which are finally subject to a more or less extensive process of caseation and ultimately become liquefied.

The pharynx, trachea, tonsils and upper respiratory tract are invaded by smooth ulcers, which are rarely destructive in character

### PROGNOSIS AND THERAPY

Some cases run a rapid course, terminating in death within 6 months after the onset of the disease. As a rule, however patients will resist for 2 to 3 years without treatment. Since the advent of sulphonamide therapy the prognosis of the disease, even of generalized forms, has improved considerably Owing to manifestations of sensitivity and intoxication, however the courses of treatment will have to be inter



838 Exogenous sporulation of P brasiliensis in culture
*(Pereira Filho—Rio de Janeiro)*

rupted and the infectious process will again be aggravated in the inter vals. As a rule treatment will be prolonged, 6 to 10 tablets of sulphadiazine or sulphamerazine being administered daily In 2 cases of mucocutaneous lesions, with evidence of lymph node and pulmonary involvement, we successfully attempted a treatment with local injections of sulphonamide ("soluseptazine"). Mixed with novocaine, the drug is infiltrated through the skin at various sites around the oral cavity It is also injected directly into the lingual muscles and into the enlarged softened or not softened, lymph nodes Local improvements were rapidly obtained with this method, the hypophonia of the patients

disappearing immediately The pulmonary lesions controlled by X ray also disappeared, though more slowly On an average, the patients were treated twice weekly 2 ampoules (0.6 g) being used on each occasion. Oral treatment with sulphonamides was considerably reduced and finally discontinued, as the patients developed a marked gastric intolerance. Two years previously one of the patients had been treated orally with sulphonamide, administered at irregular intervals, with the result that a blood transfusion was necessary

Whatever method of treatment may be used in South American blastomycosis, the precarious nutritional condition of the patients should be taken into account and vitamins and antitoxic agents should be administered simultaneously Alkalines should also be given to control gastric intolerance

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# CHAPTER 75

# JORGE LOBO'S BLASTOMYCOSIS

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Belo Horizonte

JORGE LOBO's blastomycosis or *blastomycose queloidiana* is an extremely rare, chronic affection, which so far has been met with only in Brazil. It is characterized clinically by conglomerate cutaneous lesions of a pseudo-keloid type, which may or may not be fistulous. The causative organism is *Glenosporella loboi* (Fonseca and Leao 1940) and *Glenosporopsis amazonica* (Fonseca 1945).

## HISTORY

On September 9 1930 at a meeting of the Medical Association of the Recife hospitals, LOBO reported a case of blastomycosis of 19 years standing in a patient from Amazonas, Brazil. The patient had nodules in the lumbar region, which looked like verrucous naevi. The nature of the lesions, their evolution and histopathology and the results of cultures, led LOBO to believe that the condition was due to a not yet identified species of organism. He therefore sent material for examination to the Oswaldo Cruz Institute, where FONSECA and LEAO decided in favour of this hypothesis. Further investigation definitely established the truth of their provisional assumption.

## EPIDEMIOLOGY

On account of the extremely small number of cases there are very few available data concerning the portal of entry of the infection.

JORGE LOBO's patient had been bitten by a snake 2 months before the appearance of the lesions.



839. JORGE LOBO's disease (Case of Prof. JORGE LOBO, *Rev. Med. Cirur. do Brasil* 48 (1940) 152)



840. Glenosporella loboi in tissue.
*(Nery Guimarães, Rio de Janeiro)*

**AETIOLOGY**

*Glenosporella loboi* (Fonseca and Leao 1940) and *Glenosporopsis amazonica* (Fonseca 1945) are the causative agents.

## MYCOLOGY

The following description is given by FONSECA and LEAO " parasite of the skin and subcutaneous tissue, appearing there as roundish hyalin cells with double-contoured cell walls either isolated, geminat ed, or irregularly grouped Reproduction by budding In artificial culture at room temperature on all usual media, the fungus gives rise to white colonies covered with aerial hyphae reaching, after 3 weeks 1—1.5 cm in diameter The mycelium is filamentous, septate and branched. Arthrospores are always scarce, either cylindroid or ellipsoid.

These aleuroconidia develop slowly and at a late stage, and are not



841 Glenosporella loboi in tissue. Multiplication by simple budding
*(Nery Guimaraes—Rio de Janeiro)*

liberated until the mycelium in which they are born is destroyed. Intercalary chlamydospores or chlamydoaleuria may sometimes be found"

## SYMPTOMATOLOGY

The condition is characterized by pseudo-keloid conglomerate nodules which vary in number and size they are chestnut-coloured and hard to the touch. They may become fistulous and emit a creamy pus. There is no adenitis.

The evolution is chronic. Nothing can, as yet, be affirmed as to

treatment, for the disease is rare, and none of the modern drugs employed today in the treatment of mycosis in general has, so far been successfully applied.

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CHAPTER 76

# CHROMOMYCOSIS OR DERMATITIS VERRUCOSA

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Nairobi

## DEFINITION

Chromomycosis is a chronic skin disease, which is caused by demati aceous fungi and which is characterized by extensive papillomatous and verrucous lesions, particularly confined to the lower legs, for which reason the synonym of mossy foot is most understandable. It is pointed out in this book, why the name of chromo*blasto*mycosis is erroneous. The prefix "*chromo*" is misleading in regard to the clinical picture, because it is descriptive of the causative fungus. Other synonyms are *Figueira Blastomycose negra Dermatitis verrucosa Fonseca's* *Pedroso s disease Fonseca s disease Pedroso and Carrión disease*

## HISTORY

In 1911 Pedroso — Brazil noted the presence of large dark brown to yellowish spherical bodies in a biopsy taken from a patient with nodular and ulcerated lesions of the foot and leg He was able to isolate a dark-coloured fungus. In 1915 Medlar and Lane in the United States described a disease the causal fungus of which they called *Phialophora verrucosa* In 1922 Brumpt established that the organism causing Pedroso s disease was not Phialophora ver

Some valuable parts of the paragraphs on history and aetiology have partly been transcribed from C arrion s paper in the Annals New York Academy of Sciences of 1950

rucosa, but a new species which he called *Hormodendron pedrosoi* In 1923 FONSECA and LEAO described for this fungus a second method of sporulation, which closely corresponds to the genus *Acrotheca* In 1935 CARRION and EMMONS observed that the species Pedrosoi possesses still another method of sporulation by



842 Chromomycosis



843 Chromomycosis by Acrotheca pedrosoi.

*(Orig G Costa-Belo Horizonte)*

which the conidia are produced in phialides, thus establishing its relation to a third generic form, namely *Phialophora verrucosa* The literature on the subject became extremely confusing However after years of painstaking work the synonyms of these names became firmly



844 Chromomycosis in a Surinam Negro.
*(Simons—Amsterdam)*



845 Chromomycosis of the sole of the foot by Hormodendron pedrosoi.
*([illegible])*

established and the binomial *Fonsecaea pedrosoi* proposed by NEGRONI (Argentina) has been accepted as the most convenient name (CARRION) In 1935 CARRION described a third aetiological agent of sufficiently distinct characteristics to warrant its registration as a new species, called *Fonsecaea compactum*



846 Mossy foot due to chromomycosis.

**EPIDEMIOLOGY**

At one time chromomycosis was thought to be a rather tropical disease of America, but in recent years cases have been described in Canada (BERGER) South Africa (SIMSON) East Africa



847 Chromomycosis by Hormodendron pedrosoi syphiloid type



848 Psoriasiform chromomycosis.

(PIERS) Indonesia (BONNE, VAN DER MEER) etc. in addition to MEDLAR and LANE's case in Boston.

**AETIOLOGY**

Various generically related dematiaceous fungi are responsible for most cases of chromomycosis. They may be classed in two groups



849 Acanthotic rete in the dermis.

*The first group* consists of organisms mouldy in appearance, *i.e.* Fonsecaeae pedrosoi F compactum, Phialophora verrucosa, Torula poikilospora and two Hormodendrum species described by SIMSON and O'DALY *The second group* consists of organisms which produce primarily soft dark, moist colonies undergoing what appears to be a yeast like phase in the course of their development Only two of the

organisms of this group have been published Hormiscium dermatitid is (KANO) and a black candida like species described by BERGER. It is not classified in the genus Fonsecaea Another fungus of this group was isolated by BONNE in Indonesia and again another one by CARRION in Puerto Rico

Fonsecaeae pedrosoi BRUMPT (also called *Hormodendrum pedrosoi*

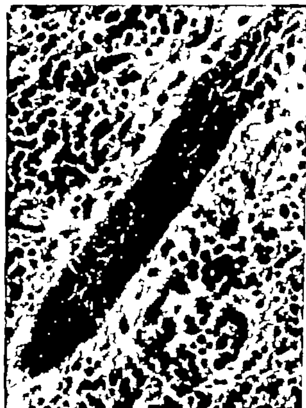


850. Acanthosis with intra-dermal granulomatous infiltrations. Note scleretic cells.

(BRUMPT), *Phialophora verrucosa* (PEDROSO and GOMES), *Acrotheca pedrosoi* (FONSECA and LEAO)) is the most common cause of chromo mycosis of which most cases have been found in the Americas and some in Europa, Africa and Asia. It has never been found in nature outside the human skin (epidermis and cutis) where it may be recog

nized as brown *sclerotic fungus cells*" which again may be enclosed in giant cells or a microabscess (URBACH and GOTTLIEB state that hormodendrum fungi are widely distributed in nature, their spores being incidentally responsible for a certain type of hay fever.) On SABOURAUD's medium after the fourth week and at room temperature, cultures may measure 5 to 6 cm in diameter

*The sporulation* is of three different types *viz* the Hormodendrum,



851 Acanthotic stripe penetrating the cutis. Note plasma cells, giant cells, and lymphocytes.

the Fonseca and the Phialophora type, but all three may occasionally be combined in the same spore head MERTIN claims to have induced specific *intracutaneous tests* in patients with chromomycosis using culture extracts of Fonsecaeae pedrosoi.



852. Mycelia from culture of Hormodendron compactum.

*(González Ochoa-Maxia)*



853. Hormonendron pedrosoi in squamae.

*(González Ochoa-Maxia)*

**Fonsecaeae compactum** (CARRION) (also called *Hormodendrum compactum* (CARRION)) has only been reported in a case from Puerto Rico and one from Tennessee (U S.A.) Its morphology in pathological tissue is essentially similar to that of Fonsecaeae pedrosoi, but it produces other colonies which grow half as rapidly as those of Fonsecaeae pedrosoi.

**Phialophora verrucosa** (MEDLAR) (also named *Cadophora americana* MELIN and NANNFELDT) has been encountered in only six cases of



854 Hormodendron pedrosoi in culture.
*(Gonzalez Ochoa Mexico)*

chromomycosis five of which occurred in the Americas and one in Algeria. Four cases originated in moderate climates. In biopsy the fungus is indistinguishable from Fonsecaeae pedrosoi, but there is a clear difference in culture growth.

## SYMPTOMATOLOGY

Chromomycosis usually affects men engaged in outdoor occupations, probably through contact of abraded or otherwise injured skin

with wood or other vegetable matter contaminated with the mycelial form of the fungi. In most cases the lower legs are affected, but lesions have been reported on the arms, hands and face. In one South-African case the disease had a perianal localization. *The initial lesion* is a papule which slowly develops into a papilloma. The process spreads by peripheral extension rather than by formation of satellite lesions, but several papules may be present from the beginning and later coalesce into larger lesions. *Hyperkeratosis* and the formation of verruciform lesions (*cf. mossy foot*) is the main characteristic of lesions of chromomycosis. In older cases very large cauliflower



855 Hormodendron pedrosoi filaments from the squamae.
*(González Ochoa—Mexico)*

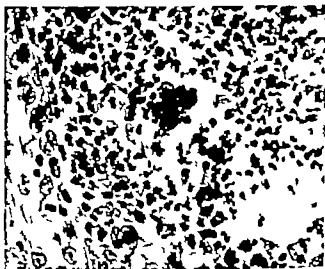
like masses may protrude from the base of the plaque. The colour of the lesions is dark purplish with a brown or dirty green tint; if there is much hyperkeratosis the colour may be more silvery or straw coloured. *Lymphadenitis* is not frequent. Older lesions may become invaded by saprophytic or pyogenic organisms and an evil smelling discharge may result. Some oedema of the affected limb is usually present. The disease is eminently chronic and may persist or slowly progress through decades until the entire extremity is involved. However there is a certain tendency to spontaneous healing. There is no tendency to systemic spread, but there is no question but that cutaneous

metastases through the bloodstream can occur (CARRION and KOPPISCH)

A somewhat different type of Hormodendrum infection has been described by SMITH from Lagos (W Africa) His cases of hormodendrum dermatitidis showed *psoriasiform lesions* of the hands and fingers, with the formation of friable subungual masses.

## HISTOLOGY

The pathology of chromomycosis appears to be the same whichever fungus may be isolated by culture. The epidermis is markedly hyper



856. Phialophora verrucosa in tissue
*(Fatal San Francisco)*

plastic Papillomatous excrescences are formed towards the surface and the widened epithelium extends acanthotic processes deep into the cutis As in American blastomycosis, an irregular meshwork of elongated and communicating strands of epithelium may be the result of the hyperplastic process The corium itself is thickened by diffuse inflammatory reaction and contains areas of granulomatous tissue in the neighbourhood of bloodvessels sweat glands and follicles, consisting of histiocytes, lymphocytes plasma cells and sometimes giant

cells. Tuberculoid arrangement is not common and necrosis and abscess formation occur rarely. Fibrosis is the final stage of the process and extensive areas of it may be present while in other parts of the skin productive inflammation is still going on. Older lesions often consist of scar tissue with scattered foci of granuloma. The "*sclerotic fungus cells*" are found in the epidermis and dermis, either free or enclosed in macrophages and giant cells. They are easily identified by the brown or black pigment they contain. The individual cells are thickened, thick walled and round, like miniature pennies. Since these fungi do not multiply by budding but by cross-wall formation and fission after enlargement, the cells are often found in little clusters, mulberry or grape-like heaps containing elements of varying size.

### DIAGNOSIS

Chromomycosis should be distinguished from blastomycosis, psoriasis, mossy conditions in yaws, leishmaniasis, filariasis Bancrofti, chromomycosis only producing sclerotic fungus cells. In the *Pimmas gass syndrome* there is a streptogenous 'mossy' foot. (BASTOS DA LUZ and VIENNA DE MEIRA)

### THERAPY

Intensive iodine treatment may effect a complete cure in many cases. Very extensive and resistant cases may require surgical interference or X ray therapy, both of which give good results.

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# COCCIDIOIDOMYCOSIS

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## DEFINITION

Coccidioidomycosis is a fungus disease caused by Coccidioides immitis (STILES). There are two forms: primary coccidioidomycosis and coccidioidal granuloma. *Primary coccidioidomycosis* is characterized by symptoms suggesting influenza and is ushered in with chills, fever and general malaise. Skin eruptions of the erythema nodosum or erythema multiforme type often occur. Pulmonary congestion and X ray abnormalities are characteristic. Primary coccidioidomycosis usually lasts fourteen to sixteen days. Sputum may be abundant or of small quantity and in which the typical spherules may be demonstrated and from which the organism can be cultured. *Coccidioidal granuloma* may be a sequel to primary coccidioidomycosis as a result of dissemination of the organisms. Coccidioidal granuloma may also occur from traumatic inoculation with spores of Coccidioides immitis.

## HISTORY

The first case of coccidioidal granuloma was reported in 1892 from Buenos Aires, Argentina, by POSADA and WERNICKE, who thought they were dealing with a protozoan infection. In North America, coccidioidal granuloma was described by RIXFORD in 1894. In 1896 RIXFORD and GILCHRIST described and discussed two further cases. The organism was considered to be a sporozoon and because of its morphological resemblance to the Coccidia, STILES suggested the

name Coccidioides. In 1900 OPHULS and MOFFIT studied coccidioidal granuloma and discovered the infection organism to be a fungus rather than a protozoan OPHULS continued his studies and further described the organism and the life cycle. Later investigators including WOLBACH continued to add more information about the nature of the parasite and the disease. These included MACNEAL and TAYLOR and MOORE, who attempted to determine the exact botanical position of the fungus ALMEIDA of Brazil, in 1930 reported cases of a disease caused by an organism which resembled Coccidioides immitis but



857 Coccidioidal granuloma resembling cutaneous tuberculosis.

differed in its method of reproduction. In Italy coccidioidal granuloma was studied by CITERRI and REDAELLI. These investigators also tried to determine the exact position of coccidioides in the classification of fungi The skin test and the soluble specific substance for it were studied by a number of investigators including DAVIS, HIRSCH and BENSON D ANDREA, JACOBSON BECK and KESSEL. STEWART and KIMURA, in 1940 endeavoured to work out a method for the standardization of the coccidioidin preparations used for the skin test.

In 1918 CUTTNER reported the presence of coccidioidal infection in

animals. BECK and TRAUM reported localized infections among cattle and sheep. STILES and DAVIS recorded the incidence and methods of diagnosis in animals.

In 1932, STEWART and MEYER isolated the organism from the soil of a ranch near Bakersfield in the San Joaquin Valley of California. DICKSON, DICKSON and GIFFORD in a series of articles in 1938 developed and explained the true nature of the disease. SMITH correlated further knowledge and developed the present concept of coccidioidomycosis.

### EPIDEMIOLOGY

Originally it was thought that the San Joaquin Valley in California was the main source of the infection. Here, the disease was known to



858 Coccidioidal granuloma resembling carcinoma.

the residents as *San Joaquin fever*, *desert fever*, or *valley fever*. Although the evidence is incomplete, the fungus is known to exist far beyond the San Joaquin Valley. The proved endemic areas of North America are Southern California to the Mexican border, Southern Arizona, Nevada, Utah, Texas and some areas of New Mexico. In Argentina the original case of POSADAS and WERNICKE was found in the Chaco area. This is the only endemic area outside of North America that has been

investigated In both North and South America, the endemic areas are characterized by an arid to semi-arid climate

Proved cases of coccidioidal granuloma have been reported from Italy the Balkans, Asia Minor and Hawaii. These cases are rare and there is no evidence to indicate that these regions are endemic areas. Case reports from Brazil show that originally Paracoccidioides brasiliensis was confused with Coccidioides immitis (MOORE)

*The incubation period* of the primary infection is from one to four weeks and the usual portal of entry is the respiratory tract In the San



859 Coccidioidal granuloma resembling carcinoma.

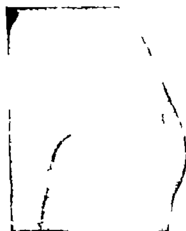
Joaquin Valley the peak of infections occurs in the dusty season when the light chlamydospores may be widely distributed The disease has no predilection for any particular race, age, or sex. The incidence of coccidioidal granuloma is greater among males than among females, probably because of greater exposure owing to their occupations. Coccidioidomycosis is not spread from man to man, from animal to man, or from animal to animal The chlamydospore not the spherule is the infecting spore. Surveys with skin testing material—coccidioidin—show an extremely high incidence of reactors among residents of

endemic areas In some Indian tribes in Arizona, the incidence of reactors is as high as 90 percent. In the San Joaquin Valley GIFFORD found that 4 out of 5 permanent residents had positive reactions.

Dissemination of primary coccidioidomycosis is extremely high in dark-skinned races especially in Filipinos and Negroes. *The death rate* from coccidioidal granuloma is more than twenty times greater in Negroes than in the white race

## AETIOLOGY

The exact position of Coccidioides in the classification of fungi is unsettled Some authors place it in the Phycomycetes, but this does not



860. Coccidioidal granuloma: subcutaneous abscess on the back

seem plausible since the characteristic mycelium of the Phycomycetes is non-septate Other investigators place it in the Fungi imperfecti

Coccidioides immitis is a fungus with *two life cycles the parasitic and the saprophytic* The parasitic cycle takes place in animals and man. The organisms occur as spherules, measuring from 10 to 60 microns in diameter Reproduction occurs by the formation of small endospores from 2 to 5 microns in diameter which escape from the mother capsule into the tissues by rupture of the capsule. These endospores then enlarge and the process is repeated. If the spherules from the

parasitic phase are planted upon a medium such as Sabouraud's agar a small tubule sprouts and typical mycelium develops. The mycelium is white and cottony; its elements are septate and reproduce by arthrospores and chlamydospores. The chlamydospores are extremely resistant to drying and when inhaled or inoculated cause infection in man and animals.

The growth requirements are simple. The organism is readily cultivated upon all types of media, Sabouraud's medium being as good as any. STEWART and MEYER used a medium consisting of ammonium chloride, sodium acetate, the primary and secondary potassium phosphates and magnesium sulphate. The organism has been successfully grown on such media as dried cactus, carrots, and decayed wood. Its origin in nature is not known, but it has been repeatedly isolated from the soil in endemic areas. EMMONS believes the reservoir of Coccidioides lies in rodents.

Coccidioides immitis grows well on practically all types of media.[1] Sabouraud's medium is quite satisfactory and may be used routinely for isolation. Body fluids, exudates, bone scrapings, sputa, etc. are suitable materials for demonstrating the spherules and for culture. The following medium with 2% agar added is satisfactory for primary cultures of clinical material:

| | |
|---|---|
| Ammonium chloride | 1.0 g |
| Sodium acetate | 1.0 g |
| Dibasic potassium phosphate | 0.2 g |
| Monobasic potassium phosphate | 0.2 g |
| Magnesium sulphate | 0.01 g |
| Distilled water | 100 ml |

After sufficient growth has occurred, the suspected culture should be inoculated into guinea pigs. After about six weeks the guinea pigs are sacrificed and the spherules may be demonstrated in the lesions found at autopsy.

*Skin tests* made with coccidioidin are analagous to the tuberculin

[1] NEWCOMER *et al.* having investigated the embryonated egg as a culture medium, believe that the cultivated spherules of the parasitic stage of C. immitis are actually normal egg-yolk spherules. Although a transient growth of parasitic spherules might be possible, it was found that the fungus vegetated in its mycelial form in the extra-embryonic membranes and in the yolk sac and not in the embryo.

tests. Sensitivity to coccidioidin develops rather early in the course of the infection and may be extremely high. The methods of preparing coccidioidin and its standardization may be found by consulting the reports of STEWART and KIMURA and SMITH. One tenth ml of the proper dilution of coccidioidin (usually 1 : 1000 or 1 : 100) is injected intradermally and the test read in 24 to 48 hours. Interpretation is similar to that of the tuberculin test. *Sensitivity to coccidioidin is permanent.*[1]

## PATHOGENESIS AND PATHOLOGY

The chlamydospores usually enter the body through the respiratory tract but they may be introduced through puncture wounds and



861 Old culture showing septate hyphae and chlamydospore formation (Saprophytic phase)

abrasions. The chlamydospores turn into spherules of the parasitic phase in the lung. The X ray appearance of primary coccidioidomycosis is strongly suggestive of the first tuberculous process in the lungs. The hilar glands are enlarged. Approximately from ten to twelve days to six weeks after exposure, the patient becomes *sensitive to coccidioidin* and will have a positive reaction to a skin test. The sensitivity to coccidioidin increases with the progress of the disease. Shortly after sensitivity develops, precipitins and complement

[1] VOGEL and CONANT have reported on a spherule antigen in a complement fixation test. They have found a rich development of the spherule following inoculation of the yolk-sac of a 10 day-old chick embryo with spores.

fixing antibodies may be demonstrated. The infection is usually localized as it is in the primary tuberculous process and the initial



862 Spherules of coccidioides in exudate from a subcutaneous abscess. (Parasitic phase)



863 Spherule in tissue
(Fatal San I [illegible])

process is calcified in a similar manner *The reaction to the coccidioidin* remains positive as in the case of the tuberculin test. The complement fixing antibodies and the precipitins gradually disappear Sometimes

single or multiple cavities may develop in the lung. They are characterized by thin walls with little inflammatory reaction around them. During the primary phase of coccidioidomycosis, erythema nodosum and erythema multiforme lesions may develop. Histopathologic studies of these lesions prove them to be sterile: they may be considered as the "ids" of coccidioidomycosis. The histopathology of the earliest lesions in the lung has never been described.

Classical coccidioidal granuloma occurs as a result of dissemination of the organisms from the primary infection. Fortunately such dissemination is extremely rare. If the organisms disseminate, all or any of



864 Spherule rupturing and endospores escaping into the tissue (Parasitic phase)

the organs may be affected. The pathological changes of coccidioidal granuloma are strikingly similar to those of a tuberculous granuloma—in both there are epithelioid and giant cells. The spherules can be readily demonstrated and may frequently be seen in giant cells. The pathology has been studied and described in detail by RIXFORD and GILCHRIST, OPHÜLS and others. Immunity to reinfection is permanent once the initial infection has subsided.

## SYMPTOMATOLOGY

*Primary coccidioidomycosis.* The majority of cases are asymptomatic. The

onset may be insidious or acute with severe prostration. Mild respiratory symptoms may be the only evidence more serious symptoms are pain in the chest, cough (usually non-productive), chills and fever The peak rise in temperature occurs in the afternoon and is usually around 101 F but may be higher Headache, malaise, anorexia, night sweats and severe pharyngitis are common. A diffuse, generalized, macular eruption occurs in some cases. The two serious complications of the disease are pleurisy with effusion and the occurrence of single or multiple cavities Haemoptysis sometimes occurs Sensitivity to coccidioidin develops early and erythema multiforme or erythema nodosum lesions may appear at this time. With these manifestations there may be a severe arthritis of any or all joints

*Coccidioidal Granuloma*. Coccidioidal granuloma mimics tuberculosis. This is particularly true of disseminated miliary coccidioidomycosis clinically it is indistinguishable from tuberculosis. The presenting symptoms depend entirely upon the site of localization. All organs have been involved Subcutaneous abscesses are quite common and may be very large or quite small. They are cold abscesses, and in this respect the disease again resembles tuberculosis There may be *bone involvement* together with involvement of the adjoining joints There is considerable rarefaction of the bones involved. Meningitis frequently occurs and is most often basilar in type and may result in hydrocephalus.

*Blood*. In primary coccidioidomycosis the white blood cells increase and may number from 10 000 to 15 000 per cu mm frequently with an eosinophilia as great as 20 per cent. The relative proportion of lymphocytes and leucocytes remains the same but there are large numbers of immature leucocytes During the recovery phase these immature forms disappear and the percentage of lymphocytes rises. Some prognostic aid may be gained from repeated blood counts.

The red blood cell sedimentation rate is of special value in diagnosis and in evaluating the course of the infection. An accelerated sedimentation rate exists in active infections, both primary and disseminated. A normal sedimentation rate in the presence of a positive coccidioidin skin test would rule out an active infection.

## DIAGNOSIS

Primary coccidioidomycosis may suggest influenza, pneumonia, or

upper respiratory tract infection. At the onset, headache may be so severe as to suggest a brain tumour Other presenting symptoms may suggest coronary occlusion, renal colic and biliary colic. The non-specific prodromal rash may be mistaken for any one of the exanthems When erythema multiforme or erythema nodosum occurs, however the clinical diagnosis is readily made. The occurrence of cavitation in the lung may resemble that resulting from tuberculosis or other cystic diseases of the lung The cysts of coccidioidomycosis however, as has been stated previously have very little inflammatory reaction about them. In the disseminated form of coccidioidal granuloma, the lesions may resemble neoplasms or the lesions of tuberculosis tertiary lues, etc. The diagnosis is confirmed by demonstration of the spherules with endospore formation in body fluids exudates biopsy specimens, etc.

## THERAPY

There is no way to prevent inhalation of chlamydospores. The prognosis for primary coccidioidomycosis, with or without cavitation is excellent In approximately one-tenth of one per cent of patients with this form of the disease the organisms will disseminate. If dissemination occurs it will do so within a few months after the initial infection. Signs of dissemination are persistence of clinical symptoms accelerated sedimentation rate, progressive extension of activity as observed in X ray films and the continued rise in the titer of complement-fixing antibodies.

*Treatment of primary coccidioidomycosis is symptomatic* Bed rest is indicated until the sedimentation rate, temperature, etc. return to normal. Salicylates may be used for erythema nodosum and erythema multiforme No form of chemotherapy seems to be of any value in the treatment of either the primary or the disseminated form.

The following treatment of coccidioidal granuloma is used by the author

1 *General supportive therapy* as in the management of pulmonary tuberculosis Where active systemic lesions are present, the patient should be at rest in bed A high calorie diet is prescribed and other medication as indicated Tuberculosis and coccidioides are frequently co-existent

2. *Coccidioidin skin tests are made* beginning with 1 1000 dilution.

onset may be insidious or acute with severe prostration. Mild respiratory symptoms may be the only evidence more serious symptoms are pain in the chest, cough (usually non productive) chills and fever The peak rise in temperature occurs in the afternoon and is usually around 101 F but may be higher Headache, malaise, anorexia, night sweats and severe pharyngitis are common. A diffuse generalized, macular eruption occurs in some cases The two serious complications of the disease are pleurisy with effusion and the occurrence of single or multiple cavities Haemoptysis sometimes occurs. Sensitivity to coccidioidin develops early and erythema multiforme or erythema nodosum lesions may appear at this time With these manifestations there may be a severe arthritis of any or all joints

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## DIAGNOSIS

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CHAPTER 78

# HISTOPLASMOSIS

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## DEFINITION

Histoplasmosis is a fungous disease of the reticulo-endothelial tissue and the skin as well as almost every tissue and organ, caused by *Histoplasma capsulatum*. It is most frequently seen among children, particularly in the male and it may reveal a most varied benign or fatal clinical and pathological picture, as is described in this chapter. Synonyms of histoplasma capsulatum DARLING are *Cryptococcus capsulatus* or *-epidermicus* CASTELLANI & CHALMERS. *Torulosis capsulatus* ALMEIDA. *Histoplasma pyriforme* DODGE and *Posadasia capsulata* MOORE.

## HISTORY

The first three cases of histoplasmosis were described by DARLING when he was searching for an American type of leishmaniasis in Panama in 1906. Because he believed the disease he described in these cases was caused by a protozoan, he gave it the connotation histoplasmosis. Subsequent studies have demonstrated Histoplasma capsulatum to be a fungus (DE MONBREUN).

## EPIDEMIOLOGY

At present the central portion of the United States appears to be the endemic focus of histoplasmosis. PARSONS and ZARAFONETIS have

pointed out that 41 of the 71 cases reviewed by them were from this area, and 10 of these cases were from the state of Michigan. The rather astounding incidence of the disease in children under one year of age has suggested to some investigators the possibility that the causative organism may be resident in or about a member of the family or be closely associated with the child's environment.

The ratio of male to female patients is about 5 to 1 (CURTIS and GREKIN) which is consistent with the predominant male incidence in most of the other deep mycoses such as actinomycosis (2 1) and blastomycosis (9 1) PARSONS and ZARAFONETIS observed in their review that among infants females are affected as frequently as males, and that on exclusion of the infant group, the ratio of infection, males to females, rose to 7 1 This disproportion strongly suggests an occupational factor in the adult cases, whereas the large group of infections in infants, combined with no disproportion of the distribution by sex would indicate an increased susceptibility in this latter group (CURTIS and GREKIN)

Investigators have demonstrated that the wild rat is susceptible to infections with Histoplasma capsulatum, but histoplasmosis in house mice appears to be uncommon. Dogs, cats, and spotted skunks have also been shown to have histoplasmosis.

## AETIOLOGY

H capsulatum is unique among fungi in that the reticulo-endothelial system is involved almost exclusively The organism is found in varying numbers within the phagocytes as a round or oval, pseudocapsular body having an average diameter of 3 microns Special stains (GIEMSA, MASSON trichome) enhance the possibility of visualizing the causative agent when there is a paucity of the organisms (CURTIS and GREKIN) Direct examination of Giemsa-stained smears of the blood or sternal bone marrow from biopsied lymph nodes or splenic punctures as well as of the material from ulcerations shows the histoplasma as a small oval body in the mononuclear cells. *Culture media* inoculated with suspected material should be retained for at least one month, the growth being relatively slow Culture mounts from such media show large, round or oval, spiculated tuberculate chlamydospores which are characteristic. At times the organism is identified by direct examination of

sputum (CURTIS and GREKIN) peripheral blood smears and material obtained by sternal aspiration. Microscopic study of *biopsy specimens* is



865 Furunculoid histoplasmosis of the lip.

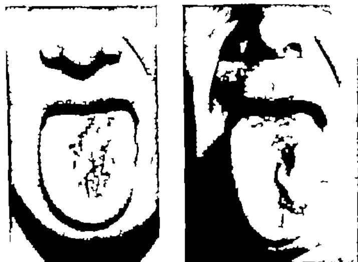


866 Ulcerat hist oplasmosis of the tongue

most satisfactory and even here the search for a single organism may at times be a protracted one The microscopic differentiation of H cap-

sulatum from the organisms of leishmaniasis and toxoplasmosis is important (CURTIS and GREKIN)

There is considerable speculation as to the mode and site of infection by H. capsulatum (CURTIS and CAWLEY) Inhalation via the respiratory tract, oral ingestion and cutaneous inoculation have been postulated, and admittedly an infection through the medium of some biting insect or by contact with animals harbouring the fungus, such as the previously mentioned rats dogs, and cats, must be given consideration.



867–868. Histoplasmosis of the tongue.
*(Francis Kelder—Ann Arbor)*

### THE HISTOPLASMIN SKIN TEST

The theory that a negative tuberculin reaction in patients with pulmonary calcifications is due to loss of sensitivity has not been generally accepted since a great number of cases have proved to be histoplasmin positive (FURCOLOW *et al.*, IAMS, PALMER, SMITH, CHRISTIE, LONG and STEARNS, ZWERLING and PALMER) (all cited from IAMS).

On the other hand more evidence is needed before certainty is obtained that Histoplasma infection ultimately leads to pulmonary calci

fication. There is still a question of the specificity of histoplasmin. Cross reactions may occur in tests with histoplasmin, blastomycin and coccidioidin.

## SYMPTOMATOLOGY

Once having gained a foothold in the human host a varied clinical and pathologic picture may eventuate. It has become increasingly apparent that the *cardinal diagnostic landmarks* enumerated by DARLING fever anaemia leukopenia, splenomegaly emaciation and chronicity are not the clinical sum total of this disease. The more commonly involved

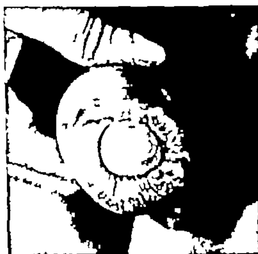


869 Papular histoplasmosis in the groin simulating mollusca contagiosa. *(Brit. J. Derm.)*

sites include the skin and adjacent mucous membranes, the larynx, lungs, liver spleen and gastro-intestinal tract, as well as the bone marrow and lymph nodes but H capsulatum distributes itself widely throughout the reticulo-endothelial system, and involvement of almost every structure and organ in the body has been reported (CURTIS and GREKIN)

Cases demonstrating prolonged involvement of only one organ have occurred while in other instances the disease process has been widely disseminated The integument is involved in approximately

one-third of the cases Punched out, persistent ulcers are relatively frequent and a papular efflorescence is not uncommon *Petechial haemorrhages* and *bullous eruptions* have been reported. *Mucosal lesions* of the nose, oral cavity and larynx, chiefly ulcerative and granulomatous in character have been encountered with a fair degree of frequency Scaling as well as verrucous dermatitis from histoplasmosis have been reported by SCHAFFER *et al.*, DE ALMEIDA and DA SILVA LACAZ (Ref MILLER *et al*) *Lymphadenopathy* is not rare and at times mimics lymphoblastoma in rather startling fashion. The invariable *emaciation* which

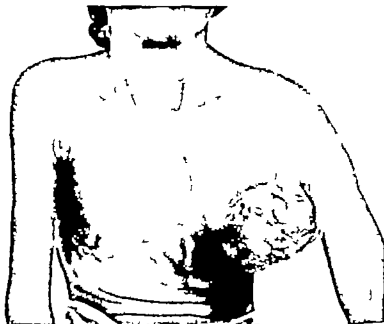


1070 Ulcerative histoplasmosis of the prepuce

accompanies advanced histoplasmosis has its origin at least in part in the gastro-intestinal lesions, with subsequent anorexia and occasional diarrhaea. *Pulmonary histoplasmosis* may at times present a fine point in differential diagnosis Clinical and roentgenographic evidence are often suggestive of pulmonary tuberculosis. Engorgement of renal glomeruli with organism-loaded phagocytes has been described. Albuminuria is a common accompaniment with cases, red and white blood cells being of less frequent occurrence. Adrenal involvement, with at times associated hypotension, has in some instances been of such

severity as to suggest the possible value of substitution therapy The clinical manifestations of the disease are protean.

Several authors have advanced the concept of *subclinical infections* with histoplasmosis, in contrast to the severe, usually fatal form of the disease, as an explanation for the high percentage of persons demonstrating a positive skin test with no demonstrable evidence of the



871 Giant swelling of two months duration in the left axilla of a Surinam woman which proved to be an atypical case of histoplasmosis.
*(Winckel Collier and Tromners Paramaribo)*

disease in an active form. RAFTERY believes the discovery of organisms morphologically identified as H capsulatum in 10 % of 436 appendices removed from children, and culture of the organism from the appendix in one such recent case to be evidence in favour of a benign form of histoplasmosis in children.

For the purpose of *prognostic classification* histoplasmosis may be arbitrarily divided into two categories. First, cases in which the portal

of entry is primary in the skin and adjacent mucous membranes, and second, those cases in which the portal of entry is a systemic one via the respiratory or gastro-intestinal system, and the cutaneous or mucosal lesions which occur are from secondary invasion (CURTIS and GREKIN). If the lesion is so localized that complete extirpation will remove the disease, a relatively unusual occurrence with histoplasmosis, as contrasted with some of the other deep mycoses, the prognosis is good. Any untreated lesion, however whether primary or secondary may go on to dissemination and eventually a fatal termination, and present methods of therapy have done little to improve this



872. Ulcerati histoplasmin reaction.

prognosis. *Subclinical or benign infections* with histoplasmosis if such an entity exists, apparently have a good outlook. A discussion of the prognosis should include mention of the fact that *histoplasmosis is found to be consistent with lymphoblastoma* in a far greater percentage of cases than can be accounted for by mere chance (RAFFERTY CAWLEY and CURTIS) that the reticulo-endothelial system is involved in both diseases that microscopic pathology suggestive of a relationship may be found with either and that the onset course, and clinical features of one may closely simulate the other (CAWLEY and CURTIS) The simultaneous

occurrence of tuberculosis is not too rare (PARSONS and ZARAFONETIS) (Ref MILLER *et al*)

**PATHOLOGY**

HUMPHREY has divided the microscopic pathologic changes which occur with histoplasmosis into three phases The first is characterized by phagocytes containing variable numbers of H capsulatum without encroachment on surrounding tissues. Subsequently necrosis occurs



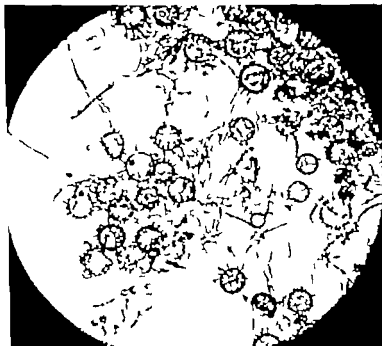
873 Culture of Histoplasma capsulatum.
*(Conant et al Man of Clin Mycology)*

at the site and during this period the continuity of neighbouring parenchymal structures is commonly disturbed, the lesion being granulomatous in character Lastly the lesion is replaced by fibrous tissue (CURTIS and CAWLEY)

**DIAGNOSIS**

Identification of the causative organism in biopsy specimens, sputum, aspirated splenic lymph node or sternal puncture material or in smears of peripheral blood is one method of diagnosis. As previously mentioned, other organisms may resemble H capsulatum closely and it is imperative that an attempt be made to culture the organism. At

room temperature, H capsulatum grows slowly on Sabouraud's medium, producing a white fluffy aerial mycelium. As the culture ages, a microscopic mount reveals the characteristic tuberculate chlamydospores These are large spores, 7 5 to 15 microns in diameter, with



874 Histoplasma capsulatum from Sabouraud's agar Thick walled tuberculate chlamydospores.

*(Conant et al., Man of Clin Myc.)*

easily discernible spinous processes projecting from the entire surface Their presence establishes the diagnosis At 37 C on blood agar the organism grows as a yeast in moist white colonies which reveal on culture mount a tiny budding yeast body varying in size from 1 to 5 microns and similar to the forms found in tissue The skin test is a third method of diagnosis, but it is not entirely satisfactory A positive cutaneous response to histoplasmin, the skin testing material, is of little or no clinical significance because of frequent cross reactions,

especially with blastomycosis and actinomycosis, while a negative reaction may be helpful insofar as it eliminates histoplasmosis as a diagnostic possibility Lastly inoculation of susceptible laboratory animals may be of aid in isolating the organism.

## THERAPY

Many agents have been used in the treatment of histoplasmosis, but the very length of the list is a mute testimony to their inefficacy Penicillin, aureomycin, chloromycetin, terramycin and the other newer antibiotics have not proved their worth, so far as can be determined. The sulfonamides and newer antimony products appear to hold most promise at present

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# CHAPTER 79

# SPOROTRICHOSIS

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Mexico D. F

## DEFINITION

*Sporotrichosis* is a chronic granulomatous mycosis due to *Sporotrichum Schenckii* (Hektoen and Perkins, 1900) Matruchot 1910 It is usually confined to the skin and subcutaneous tissues, but occasionally occurs in internal organs In the cutaneous form it produces gummatous nodules, ulcers, verrucous and acneiform lesions infiltrated plaques and erythematous and scaling patches

## EPIDEMIOLOGY

a) *Source in nature and mode of infection* Available evidence suggests that *S Schenckii* exists in plants, flowers and timber. Man acquires the infection by a thorn or a splinter The disease may also be contracted from bites of animals, acting as mechanical carriers, and laboratory infections have been observed frequently Helm and Berman recorded an important epidemic among workers in South African gold mines caused by infected timber. In Mexico contagion is frequently noted among people who handle packing straw

b) *Distribution and seasonal incidence* It is worldwide but with a differing incidence according to diverse geographical regions and specific climatic conditions. It is a relatively rare disease in the United States of America, where Benedek has recorded 206 cases since the first one reported by Schenck in 1898 in that country Forster (1924) had remarked that the disease is endemic in the Mississippi River basin. In

Mexico it is undoubtedly the most common deep mycosis in the last few years over 300 cases have been observed in Mexico City and up to the present three regions with high endemic rate have been discovered in Guerrero Guanajuato and Nuevo Léon. There is not enough information about the incidence in Central America, so that its importance is difficult to establish. This mycosis has been found in every country of South America, especially in Brazil (ALMEIDA) and Colombia (SILVA). In South Africa, BROWN *et al* (1947) collected more than 2800 cases which were reported in three and a half years In Europe most of the



875 Sporotrichotic chancre on the wrist and lymphatic spreading type showing the gummatous ascending form.

cases have been observed in France, but in almost every country the disease has been recorded NORDÉN (1951) states that Norway is the only Scandinavian country in which sporotrichosis has been encountered

BROWN *et al* (1947) remark that the maximum incidence of sporotrichosis in the South African mine of Venterpost, occurred during the months of the greatest heat and humidity and MACKINNON (1949) on the basis of 32 cases recorded in Uruguay between 1929 and 1948 concludes that sporotrichosis is contracted during the months with

high values of relative humidity (98 to 100 per cent.) and heat therefore the geographical distribution of sporotrichosis might be explained by weather conditions

c) *Incubation period, Occupation Sex Age and Race* The incubation varies widely the average is 8 to 30 days but periods from 1 to 6 months were recorded in the South African epidemic. To a certain extent it is an occupational disease of agricultural manual workers and florists and people who are in contact with vegetable matter contaminated with the fungus, such as timber and packing straw It predominates in males and the average has been reported to be between the second and third decades but many cases have been recorded in children and in aged persons All races seem to be equally susceptible.



876. Gummatous ascending form of sporotrichosis on the forearm.
*(Orig. G Castro-Belo Horizonte)*

## SYMPTOMATOLOGY

### 1.—CUTANEOUS LOCALIZATION

In cutaneous sporotrichosis the primary lesion, or inoculation chancre, appears as a rule on exposed parts of the skin, commonly on the hands, sometimes on the face, neck and foot. The initial lesion may be a simple acneiform pustule, a little gumma or abscess, an ulcer or a verrucous plaque (Fig. 875) One must make a differential diagnosis from boils carbuncles and pimples, and from syphilitic chancre or verrucous tuberculosis.

The different clinical varieties of cutaneous sporotrichosis result from the evolution which the *sporotrichum* may follow after the cutaneous chancre It all depends on whether or not there is spreading of the fungus from the primary lesion, and on whether the dissemination

takes place through the lymphatics or blood vessels. The following table illustrates the clinical classification of cutaneous sporotrichosis.



877 Lymphatic spreading type showing the gummatous ascending form with nodules and ulcers at different stages of evolution.
*(Lange-Ursen)*

| | Type | Forms |
|---|---|---|
| CUTANEOUS SPOROTRICHOSIS | Lymphatic type | Gummatous ascending on extremities |
| | | Gummatous in other regions |
| | Fixed type | Ulcerative |
| | | Verrucous |
| | | Acneiform |
| | | Infiltrated plaques |
| | | Erythematous and scaly patches |
| | Haematogenous type | Gummatous disseminated over the cutaneous surface |

a) *Lymphatic type.* This type represents the classical picture of the disease. A few days, or weeks after the chancre appears one or several nodules are found along the lymphatics which correspond to the site of the initial lesion, appearing one after the other. They grow rapidly in size and will soften originating abscesses that later open and some become occluded with sero-crusts while others are transformed into ulcers, and finally some of them heal. The lymphatic vessels connecting the elements described are thickened and palpable as cords and it is quite interesting to note that the correspond-

ing lymph nodes are rarely involved. A peculiar sign of these nodules, abscesses or ulcerations, is a purplish or cyanotic tint whose histopathological formation will be explained later There are remarkably few symptoms, and the patient is usually afebrile.

When the initial lesion takes place on the extremities, usually the hands, it originates the clinical form denominated *gummatous ascending of extremities* whose picture is so well defined that the clinical diagnosis is easily made. The gummatous lesions or their sequelae follow almost straight lines, along the length of the limbs (Figs. 876–878) In the differential diagnosis of this clinical form one must take into consideration, perhaps only the primary sore and the nodes or ulcerations of



878 Gummatous ascending form in which the ulcerated nodules have been covered with crusts.

tularaemia, but in this disease the lymph node enlargement is the rule, while in sporotrichosis it is the exception and the patient is afebrile. The infection by cocci specially *Streptococci* should also be taken into account, but in that case the incubation period is very short, there is no inflammation of the lymphatic trunks, but there is reticular lymphangitis with enlargement of lymph nodes and the general health is seriously affected

In *gummatous forms of other regions* the inoculation chancre and the nodules, that are formed along the lymphatics, present the same aspect as those just described, except that the nodules or the resulting lesions do not show any arrangement in ascending lines, but appear



879 Lymphatic spreading type, gummatous form on the face

*(Núñez Andrade—México)*



880 Lymphatic spreading type, gummatous form on the face with ulcerated nodules.

*(Latapí—México)*

irregularly in the vicinity of the primary lesion (Figs 879–882) In this clinical form differential diagnosis should be made from colli



881 Sporotrichosis of the face gummatous case.
*(Latapí–Mendez)*



882 Gummatous form in the face
*(Latapí–Mendez)*

quative tuberculosis, especially when it appears on the neck (Fig 883), from syphilis, and from actinomycosis of the face Histopathology and guinea pig inoculation will reveal the tuberculosis

serology will help to differentiate syphilis, and actinomycosis will be discovered by the finding of the actinomycotic granules

b) *Fixed type* The different clinical forms related to this type of sporotrichosis are characterized by the fact that the parasite, when it enters into the body and produces the primary lesion, remains there, "in situ" it does not spread, and there is only growth of the primary lesion. Probably this fixed type is due to the immunologic defences of the host, inasmuch as we have observed the reproduction of a fixed form by autoinoculation from another fixed lesion, but in an anatomic region without lymphatics, in connection with the first one. Some of the



883 Gummatous form of the neck similar to scrofuloderma.
*(Núñez Andrade-Meyer)*

clinical forms included by DE BEURMAN and GOUGEROT in "epidermic sporotrichosis" correspond to the fixed type Occasionally after months or years a fixed lesion may spread through the lymphatics and in that case we observe the gummatous lymphatic lesions superimposed on the primary fixed type

Clinical forms of the fixed type are *ulcerative* and *verrucous* as the most frequent, and the *acneiform infiltrated plaques* and the *erythematous and scaling patches* as rarities. In the *ulcerative* form the primary lesion becomes a small ulcer which slowly and gradually enlarges until it reaches a variable extension, usually no more than 10 cm It is covered with sero-sanguinolent or impetiginous crusts, and its bord

ers acquire a purplish colour, Frequently the ulcer is covered with verrucous vegetations, so that a mixed ulcero-verrucous form results (Fig.884) Differential diagnosis must be made from syphilitic and tuberculous ulcerations from chromoblastomycosis and blastomycosis, pyodermite végétante and epithelioma.

The *verrucous* form generally appears on the face, in a region close to the buccal and ocular commussures or on the nose (Fig 885) It adopts the appearence of warty or papillomatous excrescences To a certain extent these are mild forms of sporotrichosis they grow very slowly and do not produce large lesions, inasmuch as new elements appear when others have already healed. Differential diagnosis should



884 Fixed type of sporotrichosis, ulcerative form covered with crusts.

be made especially from tuberculosis verrucosa, warty growths, condylomata and epithelioma.

The acneiform sporotrichosis usually affects the face, involving the eyelids, nose forehead and chin. It is very frequent in Bogotá, according to SILVA but in Mexico this clinical form also exists. It presents a picture similar to acne vulgaris or to a pyoderma, with papules of varying sizes that soften and break discharging a seropurulent material which dries forming impetiginoid crusts (Fig 886)

The form of *infiltrated plaque* resembles sarcoid, tuberculoid leprosy and keloids from pyogenic or tuberculous lesions. The erythematous-scaly form is noteworthy because it is a very superficial lesion which looks like a flat, rough, erythematous patch covered with

scales resembling a psoriasiform plaque or a dermatophytosis.

c) *Haematogenous type*. Although some cases have been described in the United States of America, Austria, Germany, Norway, Mexico, Brazil and South Africa, this type is found more frequently in France. It is a subacute or acute form of sporotrichosis in which it is



885. Fixed type of sporotrichosis, verrucous form.

(Nuñez Andrade—Mexico)

difficult to recognize the primary lesion. The first symptom is the appearance of numerous hard subcutaneous nodules, similar to those of the lymphatic spreading type, except that in this haematogenous dissemination the nodules are scattered all over the body. They may vary considerably in number, may have the size of a pea or a hazel nut, and sooner or later they become softened with a central depression. The overlying skin is involved in some of them, acquiring a purplish tint

and when punctured when they open spontaneously a viscid pus comes out when perforation occurs they form ulcers just like those of the lymphatic type. Patients with this haematogenous disseminated type are acutely ill, and unless treated they die in a cachectic state with visceral involvement. Differential diagnosis must be made from generalized gummatous syphilis from gummatous forms of tuberculosis and from tularaemia

When cutaneous sporotrichosis has existed for a long time, especi-



886. Sporotrichosis similar to pyoderma.

*(Orr G Carta-Bela Horizonte)*

ally in the gummatous lymphatic forms, it presents a clinical pattern which may be confusing The skin lesions appear as infiltrated plaques—with nodular, crusted or papillomatous elements, in which a secondary infection complicates the clinical picture (Fig 887). The lymphatic and fixed forms intermix, but even in this condition it is possible by means of accurate observation and a careful anamnesis to recognize the original type of sporotrichosis. Healing of these extensive lesions occurs in the form of large keloids causing deformities

and limitation of movement. Early and limited lesions also leave, at times, keloid formations.

2.—INTERNAL SPOROTRICHOSIS

Internal, systemic or visceral sporotrichosis is very rare. The clinical forms are a) *primary* b) *concomitant* with the gummatous haematogenous spreading type and c) *secondary* to neglected lymphangitic or fixed types.

As *primary* internal forms of sporotrichosis the pulmonary the



887 Sporotrichosis with crusts and papillomatous plaques.
*(Oar G Carlo-Belo Horreate)*

testicular and epididymal localizations have been recorded. In these forms it is generally unknown how the fungus penetrates, and there are no constant clinical data which may indicate the portal of entry only by elimination and by laboratory means can one arrive at the diagnosis.

The *concomitant* form with the gummatous haematogenous spreading type, is the most frequent. The majority of internal forms belong to this type. Cases with involvement of all viscera or tissues have been described, which means that no organ is immune to *S. Schenckii*. The

clinical diagnosis is guided by the gummatous lesions scattered over the body

In the form *secondary* to cutaneous lymphangitic or fixed types, the infection spreads by continuity to deep tissues, and in that manner lesions of nose, mouth, pharynx, bones of the orbit, and the eye itself have been described which started as cutaneous (Fig 888). Also in these cases, the cutaneous localization confirms the clinical diagnosis

#### DIRECT EXAMINATION

*In the experimental or natural sporotrichosis of animals the fungus*



888 *Sporotrichosis of the eye secondary to gummatous form on the face (González Ochoa–Mourão)*

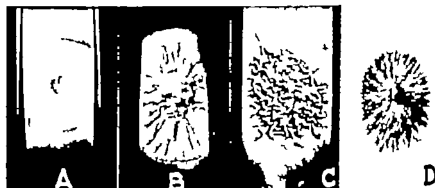
appears as fusiform elements from 3 to 7 by 1 to 2 μ, named "cigar bodies" (Fig 890) these formations would become transformed, according to NORDÉN (1951) into round or ovoid budding cells and rings that are also present in pus and constitute the "tissue phase" of the fungus. In human sporotrichosis the tissue phase takes polymorphic aspects as coccoid elements, rings and hollow spheres which are very difficult to identify and are confused with nuclear and cellular débris (GONZALEZ OCHOA and SOTO PACHECO 1950) Occasionally it is possible to see these formations abundantly and sometimes even cigar

bodies and fragments of hypha-bearing conidia, when the host's defences are lowered. Also in very rare cases radially arranged projections are observed, around an acidophilic spherical cell, with double membrane, which were thought formerly to be produced by a different species of *Sporotrichum*: *S. asteroides*, but nowadays it is known that they originate from the only species pathogenic to man, *S. Schenki*.

**CULTURE**

*S. Schenki* grows easily in all media. It adopts two types, according to the growth conditions, the "mycelial phase" and the "yeast phase".

a) *Mycelial phase*. In Sabouraud's medium, at room temperature, it




889. Different types of S. Schencki colonies on Sabouraud's glucose agar at room temperature. Mycelial phase.

appears as small white colonies surrounded by a peripheral fringe of thin filaments that may be clearly observed with a magnifying glass. As growth increases, the surface of the colony becomes folded or wrinkled and takes a membranous and moist appearance; the colour may vary from cream to black, Figs 15, taking, in very rare strains, a filamentous blackish aspect (Figs. 889 d). The pigmentation of some strains was once regarded as a means of differentiating species, but it has been frequently observed that one strain goes through all the shades of colour. Microscopically it is characterized by a delicate mycelium of 2 μ, branching and septated bearing conidia laterally or in groups at the ends of lateral branches, forming rosettes (Figs. 891 and 892). The conidia are pyriform, spherical or ovoid, from 3 to 6 by 2

to 5 μ and are inserted on the filaments by a short stalk these conidia are smaller than those of most saprophytic Sporotricha (EMMONS 1948).

b) *Yeast phase* This was obtained at first by culturing the fungus in inspissated human serum (LUTZ and SPLENDORE 1908), and later in many diverse media and varying experimental conditions It is of some interest to mention that the yeast phase is also obtained by culturing sporotrichotic pus in saline plus penicillin (GONZALEZ OCHOA and SOTO PACHECO) and by transplanting the mycelial phase



990 Experimental sporotrichosis in the mouse. Gram-stained smear from pus showing fusiform "cigar bodies"

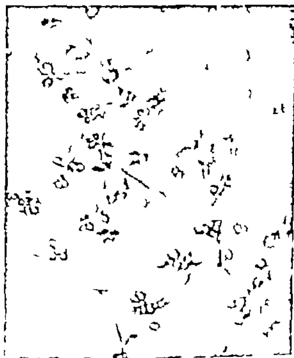
in Sabouraud s medium plus penicillin (GONZALEZ OCHOA and SALINAS) Microscopically the yeast phase shows yeast like elements similar to those of Candida

## IMMUNOLOGY

a) *Serology* According to NORDÉN who has performed a careful study of agglutination, complement fixation and precipitin reactions, on eleven cases of human sporotrichosis the precipitin test seems to be the most sensitive the complement fixation may perhaps indicate widespread or deep-seated disease whereas lesions of limited extent

may show no antibody response. But even the precipitin test has no practical value for diagnostic purposes because when tried in 8 patients it was negative in 3 with active lesions.

b) *Hypersensitivity* Patients with sporotrichosis, with limited as well as extensive lesions practically always give a positive skin reaction with a polysaccharide obtained from *S Schencki* culture (GONZÁLEZ



891 Microculture of S Schencki with microconidia. *(Hart—Caracas)*

OCHOA and SOTO FIGUEROA) This cutaneous test has been evaluated in hundreds of cases invariably showing its high specificity

**DIAGNOSIS**

a) *Culture* The absolute diagnosis ultimately depends upon the recovery of the causative fungus by culture. Pus collected from ulcerative lesions preferably from an abscess which has not yet broken or frag

ments and scales of verrucous and scaling lesions should be streaked on Sabouraud's glucose agar slants, and maintained at room temperature. In general the growth is recognizable within 3 to 6 days, but bacterial contaminations delays it. Very soon the culture will adopt the macroscopic and microscopic morphology of the mycelial phase mentioned.

b) *Direct examination* This has no practical value for diagnosis, because the "asteroid bodies" are too infrequent, and the tissue phase of the fungus is easily confused with cellular débris

c) *Skin test* The intracutaneous injection of 0 1 ml of the mention

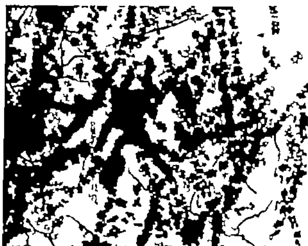


892. Delicate mycelium bearing conidia.

ed polysaccharide (GONZÁLEZ OCHOA and SOTO FIGUEROA), at 1 2000, elicits in 48 hours in active or dynamic cases of sporotrichosis, an erythematous plaque of at least 3 cm, accompanied by a vesicle in some hypersensitive patients. No false or cross reactions with other mycoses have been observed This test is now used in Mexico for the diagnosis of sporotrichosis

d) *Animal inoculation* The intraperitoneal or intratesticular inoculation of pathological products in male white rats leads, after 2 to 3 weeks, to peritonitis and orchitis the described formations of the tissue phase can be seen by microscopic examination

c) *Pathology* There is a granuloma, with small purulent foci surrounded by histiocytes epithelioid cells, lymphocytes, plasma cells and, sometimes, giant polynucleated cells There is also vascular neoformation, and the vessels show endothelial tumefaction and hyperplasia of their wall. Frequently macrophagic cells are found enclosing small, basophilic bodies, round or fusiform, some of which are probably the parasites quite often indistinguishable from nuclear débris



893 Conidia laterally inserted along the filame

THERAPY

The only drugs which have proved their merit as specifics are the iodides The mode of action is unknown. Potassium iodide in ascending doses and up to the point of tolerance, controls the cutaneous sporotrichosis. It does not act by fungicidal mechanism since it has no activity *in vitro* at 10 per cent., and does not prevent the infection in rats, although it is curative (DAVIS) It is best to administer the iodide for a period of about 3 weeks after the visible signs of the disease have been subdued. A practical method is to begin with 0.50 g of chem. pure potassium iodide and to increase daily until reaching 3 to 4 g this should be administered in milk and after meals The sulphonamides act *in vitro* against *S Schenki* (GONZÁLEZ OCHOA & ZOZAYA,

NOOJIN and CALLAWAY), but the results in patients are disappointing Antibiotics should not be used, since CAMPBELL and SASLAW discovered that the growth of *S Schencki* is stimulated by streptomycin, and GONZÁLEZ OCHOA and SOTO PACHECO found that penicillin acts as a growth factor for the fungus.

Patients with high sensitivity who do not respond to iodides rapidly it is useful to desensitize with increasing amounts of saline dilutions of polysaccharide. Surgery should be avoided X ray therapy sometimes produces favourable results

Blood dissemination and visceral forms are always severe when the visceral invasion is extensive the patient dies in spite of the iodides. In these cases iodides should be administered cautiously after previous desensitization.

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## CHAPTER 80

# ACTINOMYCOSIS

## (Nocardiosis)

H. GOUGEROT

Paris

### DEFINITION

Actinomycosis is a ubiquitous, chronic, deep mycosis common in man and in cattle, and caused by aerobic and anaerobic fungi of the genus *Actinomyces (Nocardia)*. It is characterized by the formation of nodose lesions which may fistulate and eventually form abscesses, producing yellow granules or pus containing filaments. The disease is rare among children.

The most important causative fungi in this group are,

*Actinomyces bovis* Harz (1877), *Nocardia asteroides* (Eppinger) Blanchard (1896) and *Nocardia madurae* (Vincent) Blanchard (1896).

Synonyms are: *for A. bovis*: *A. israeli* Dodge, *Discomyces bovis* Rivolta, *Streptothrix actinomyces* Rossi-Doria and *Nocardia actinomyces* Trevisan.

*for N. asteroides*: *A. asteroides* Gasperini, *A. gypsoides* Henrici Gardner and *Cladothrix asteroides* Eppinger.

*for N. madurae*: *A. madurae* Lachner Sandoval, *N. indica* Chalmers-Christopherson, *Discomyces madurae* Gedoelst and *Streptothrix madurae* Vincent.

### HISTORY

Actinomycosis was first studied in cattle by Rivolta (1866) who recognized the parasitic nature of the granules, which had already been described by Davaine in 1850.

### AETIOLOGY AND PATHOGENESIS

Patients are most frequently infected in the open air *e.g.* during agricultural labour, and especially by plants gramineae, fruits, or dead wood or through chewing the stems and blades of gramineae. In the majority of cases the disease starts at the mouth or the pharynx. Nocardiae found in nature, or in the mouth, are often not pathogenic.

### CLINICAL FORMS

The most frequent clinical forms are cervico-facial actinomycosis and the so-called "madura foot"



894 The ray fungus granule of actinomycosis.
*(González Ochoa–Varela)*

### I. CERVICO-FACIAL ACTINOMYCOSIS ("LUMPY JAW")

From the aetiological point of view there exist three different opinions *i.e.*

a. British authors (WRIGHT *et al.*) believe that the only parasite in cervico-facial actinomycosis is *Cohnistreptothrix israeli* KRUSE.

b. Others—I share this opinion—consider this unicistic conception to be exaggerated, in which they are supported by PINOY's statistical

data (Institut Pasteur d Alger) they admit that *C israeli* is most frequent, but *A. bovis* HARZ may also be met with.

c. Others again (GASPERINI *et al*) incline to the opposite view and suggest that the name *Nocardia (Actinomyces) bovis* does not cover kindred but distinct parasites differing both in the cultures and in the inoculations into animals. GASPERINI *et al* distinguish three types of *A bovis* *i.e.* *A sulphureus* *A albus* and *A luteoroseus* (from the colour of their respective cultures)

The primary lesion is usually in the mucosae of the mouth or the pharynx, via the gums or carious teeth, or even via the tonsils. In some cases the initial lesion has other localisations *e g* submaxillary



895 Ulcero-nodose actinomycosis called "lumpy jaw"

and cervical, peripharyngeal, oesophageal, parotic, or even in the mediastinum and lungs

When fully developed the lesions consist of subcutaneous nodosities rarely isolated, more often contiguous, mammillating the region involved partly fusing into a mass as hard as wood (*"phlegmon ligneux"*) more or less embedded in a soft oedema.

They are of unequal size 5—20 mm in diameter hardly if at all, painful the covering skin is a pink or violet-pink colour

The skin more or less quickly adheres to the nodosity the latter does not or only very little, adhere to the deep tissues. The fistules discharge serous pus containing "yellow grains" Pain is minimal, providing there is no secondary infection. *Trismus* is frequently

present when the oral muscles are affected, and in the so-called "wooden" type. *Adenitis* is rare, except in secondarily infected cases.

*In the subcutaneous ulcerated form* (rare), the skin may be largely destroyed over an area of many centimetres.

*The cutaneous nodular form* shows the same characteristics only more superficial.

*In the ulcero-vegetative form* the ulcerations become papillomatous, and by their hardness simulate cancerous growths.

*In the subcutaneous form* with abscesses the larger nodules produce large abscesses, which may or may not ulcerate.

*In the subacute anthracoid dermic form of* MAJOCCHI, numerous nodules become confluent, rapidly fistulated, and simulate a carbuncle or anthrax. But instead of healing, like a carbuncle caused by *Staphylococcus aureus* the lesion becomes chronic, with suppuration containing "yellow grains

*In the acute pseudo-phlegmonous febrile form of* GOUGEROT and MATHIEU the onset is acute with high fever the lesion is usually open, resembling a phlegmon, but the fistules become endless, with pus containing "yellow grains"

It will be seen from the above that all these forms are polymorphous enough but they have certain symptoms in common which allow of a clinical diagnosis, which, however should be confirmed by finding the parasite.

## SYMPTOMATOLOGY

The chief common symptoms are,

a. the nodular shape, and usually conglomerated state, of the lesions

b the diffusion, and wood-like hardness of the infiltration, which resembles that of cancer but is coupled with phlegmonous reactions

c. the adherence to the skin, with bluish or reddish-blue colour on which the nodules are seen red- or purple-coloured

d. the large number of softened nodosities and fistules, but their small size among the ligneous infiltrate

e the thinness of the skin over the softened nodules, through which

a greyish, gelatinous matter, sometimes with yellow spots, may be seen

f the narrow and irregular shape of the fistules, and their friable, yellowish or violescent edges

g the slowness and poorness of the suppuration, with clotted, often foetid serous pus containing "yellow grains" the latter may be seen with the naked eye they are sometimes greyish, sometimes sulphur yellow sometimes brownish either round or mulberry shaped brittle, and easy to squeeze

h. the frequency of a diffuse oedema at the edges of the nodules



896 Ulcero-nodose or gummatous multifistulous form of facial actinomycosis
*(Gonzalez Ochoa–Urueta)*

i. the general painlessness of the lesions, which are sensitive only to palpation

j the slow "cold" evolution, which for a long time does not affect the patient's general condition

k. the tendency to local subcutaneous invasion, and to attack muscles and bones

l the absence of adenitis

m. the potassium iodide test therapy or better still, X ray treatment

*Roentgenograms* reveal no involvement of the bone except in chronic cases when periostitis and osteomyelitis may occur

### II. MEDIASTINAL OR THORACIC ACTINOMYCOSIS

Mild, irregular fever and cough may be the initial, inconspicuous symptoms of thoracic actinomycosis originating from aspiration of infected sputum from the mouth. The condition may be clinically similar to tuberculosis i.e with pulmonary abscesses haemorrhagic sputum involvement of the pleura loss of weight, and dyspnoea. However, examination of the sputum will reveal the fungous elements. Contrarily to tuberculosis, actinomycosis affects the thoracic wall, and results in multiple sinuses producing "fungous pus ". X ray



897 Ulcero-vegetant actinomycosis of the buttocks (Ulban–Peri )



898. Recto-ano-genital actinomycosis.

examination reveals massive areas in the lung bases which might more readily be taken for a neoplasm. The pleura and the ribs may be involved, and there may be accumulation of fluid

### III. ABDOMINAL ACTINOMYCOSIS

When the sputum is swallowed, fungi may enter through the mucous membranes of the intestines Metastases from the mediastinum and thorax (and vice versa) may also occur. Intestinal actinomycosis may initially resemble either appendicitis or intestinal neoplasm. Any abdominal organ, and even the vertebrae, may be involved. Almost the only reliable diagnosis is by means of an exploratory laparotomy

## IV RECTO-ANO-GENITAL, ULCEROUS OR FISTULOUS ELEPHANTIASIC ACTINOMYCOSIS

Since 1910 GOUGEROT has collected more than 20 observations of the above localizations which simulate tuberculosis and Nicolas-Favre s disease. They are characterized by elephantiasic tumours with ulcerations, fistules usually without adenitis eventually becoming chronic.

## V MYCETOMA PEDIS OR MADURA FOOT

See Chapter 81



899 Histology of juxta-articular node in which the parasite has been called "forme incolore de la nocardia carougeaui de Madagascar (GOUGEROT )

## VI ABSCESSES AND GUMMATA (EITHER SINGLE, OR MULTIPLE AND SCATTERED)

Abscesses and gummata, either single, or multiple and scattered may be caused by different Nocardiae, called either N majores" or "minores (or "breviores" as, for instance, N *asteroides*) They resemble all other gummata syphilitic, tuberculous sporotrichotic, etc They are often accompanied by visceral symptoms that may end fatally *e g* by meningitis or other visceral localizations.

## VII JUXTA-ARTICULAR NODOSITIES

First described by LUTZ, in his letter from Honolulu (1891) and afterwards by

*Syndrome des nodosités juxta-articulaires dues à la Nocardia Carougeaui de Madagascar* Segment d'une gomme avec des grains volumineux incolorables, d'où le nom de Mycose à "ombre" incolorable par les colorants spéciaux, teintée seulement par des colorants indifférents" tel que le bleu

JEANSELME (1904). This disease, again, is an anatomo-clinical syndrome caused by many different organisms not only *Nocardiae* but also *Aspergillus Spirochaeta pallida*, *Treponema pertenue* (yaws), and even *Filariae* (*Ceylon*). I have myself described a *Nocardia Carougeaui* from Madagascar.

They are gummatous nodosities fibrous and indurated rarely fistulized or ulcerated they have the size of a nut or smaller and are irregularly disposed around the big joints and their bony projections (hands, knees, elbows). They are painless and have very slow chronic evolution.

VIII. EPIDERMAL NOCARDIOSIS

The lesions are very peculiar in their clinical aspect, and are only parasitologically related to the foregoing forms.

*Erythrasma* caused by Nocardia minutissima its culture has been discussed in Chapter 59 It is supposed to have been obtained by MICHELLI, DUCREY and REALE, by positive inoculation of this culture in man. The clinical aspects of the affection are well known It is generally localized in the genito-crural folds, producing large patches with round edges the epidermis is brownish or reddish-brown, slightly folded, and feels unctuous to the touch, something like talcum, with very thin, dusty squamae. The affection is easily distinguished from trichophytosis (Hebra's marginated eczema"), in which there are vesicles, and from pityriasis versicolor

*Erysipeloid* was discovered by PASTEUR and THUILLIER (1883) and investigated again by ROSENBACH (1884). The parasite has been differently named *Actinomyces thuillieri A. rosenbachi* and *Erysipelothrix porci* (ROSENBACH). It does not only occur in pigs, but may also be found, as a saprophyte, in fish and in crustacea. It is extremely pathogenic in pigeons. In man, it occurs especially in workers handling pigs, chiefly producing lesions of the hands or forearms and sometimes of the face. These lesions spread similarly to erysipelas (hence the name), with central regression, centrifugal progression, rarely an actual "bourrelet" spontaneous healing, usually without general symptoms (except when there are complications such as fever arthritis, or even meningitic symptoms).

## MYCOLOGY

These fungi belong to the group *Microsiphonae* (VUILLEMIN) The *anaerobic type* consists of only one species, *A. bovis* HARZ, whilst *the aerobic type* comprises several Nocardiae *N asteroides N madurae* etc. All fungi of both groups are Gram-positive the *A bovis* is non-acid-fast some of the Nocardiae are acid-fast.

1 The mycological diagnosis may be difficult for the secondarily infective organisms may mask the actually causative Nocardiae, which should show granules, *i.e.* branching bodies with "clubs for which reason the term "*ray fungus*" has been coined.

The macroscopic discovery of grains is not sufficient for purulent particles may contain bucco-pharyngeal filamentous parasites second

**SERODIAGNOSIS**

Serodiagnosis may be used when the culture fails to yield results or has proved impossible (WIDAL and ABRAMI)

Direct sero-agglutination is impossible, because no homogeneous cultures of Nocardiae can be obtained. One is compelled to use co-agglutination with Sporotrichum beurmanni spores (taken from a culture on Sabouraud s agar 4—12 weeks old)

The technique is the classical one, as described by WIDAL and SIGARD for typhoid fever

These co-agglutinations are done with actinomycotic sera at dilu tions of 1 10—1 200 or more.

Complement fixation (as in Bordet Wassermann s reaction) may be done either with an antigen prepared from Nocardiae or more easily with one prepared from *Sporotrichum beurmanni*

These co-fixations and co-agglutinations are not specific, and enable only a group diagnosis of mutually different mycoses.

*Animal inoculations* of sputum, either subcutaneous or intraperitoneal in guinea pigs may be rarely necessary to establish the diagnosis.

**THERAPY**

The treatment of actinomycosis is often difficult. The efficiency of potassium iodide per os (or in any other way) is merely legendary in most cases the iodide is hardly if at all, effectual and high doses (8—12 g daily) must be given. In fact, it is merely a supplementary treatment, not the principal one.

The therapy should be applied in different stages, *1st First stage* X ray therapy (Japanese method of SHIOTA) This is the best method and may produce remarkable cures. GIRAUDEAU in my clinic, applies 3 irradiations (about 200 r 90 kV 2 mm aluminium filtration), separated by an interval of one week. If necessary he repeats this series one month afterwards and even a third time but then there is a risk of telangiectasies

The following antibiotics have been tried

Penicillin. WALLACE, HERELL, NICHOLS, and HEILMAN (Rochester), in 12 cases, had 2 failures 2 cures and 8 doubtful results after 18 months treatment HAMILTON and KIRKPATRICK have used doses as high as 6 million units DEBRE, KAPLAN and ROTLR cured a case

of cachetic visceral actinomycosis with one million units per day

Sulphonamides. BERTHELON and VALIN in animals (bovines), observed cures with fontamide.

ARNOLD and AUSTEN successfully treated a penicillin-resistant case with 1 g of diazone per day

Streptomycin may be tried (1 g per day for 10 days) It is most



901 Actinomycosis of the right shoulder

*(Gonzalez Ochoa—Mexico)*

interesting when other antibiotics have failed. This treatment may be continued, the dose being increased up to 2 or 3 g per day for 2 or 3 months.

Heliotherapy and ultraviolet rays may be combined with the above, as in fistulized tuberculosis.

*Second stage* In combination with potassium iodide therapy

vaccines may be used either stock vaccines (WRIGHT) or better auto-vaccines when the culture of the organism has been made.

*Third stage* If after two months, the above trials have proved unsuccessful, local treatment should be tried, *i.e.* local injections of antiseptics.

Experience has shown that the following are most active iodine or iodide solution $HgCl_2$ arsenous acid creosote formaldehyde, and copper sulphate.

Local injections should be made into the indurated masses at multiple points and with previous local anaesthesia. It should, however be borne in mind that some of the above antiseptics are caustic.

*Fourth stage* If these local treatments, continuing the general treatment (potassium iodide and X rays), also prove unsuccessful, surgical methods may be tried If possible, complete extirpation (as for a malignant tumour) is best if not, apply incision and cleaning up of the foci by thermo- or electro-coagulation, followed by antiseptic applications such as iodine vapours tincture of iodine formaldehyde a 10 per cent. $ZnCl_2$ solution a 1 per cent. $HgCl_2$ solution, or creosote.

In all these mycoses relapses are frequent when the treatment is discontinued too soon. Cicatrization should be carefully watched, and the general treatments if proved successful, should be pursued for weeks and even months, with only brief intervals.

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CHAPTER 81

# MADURA FOOT

CARLOS CASTANEDO Y PARDO
Havana

## DEFINITION

Madura foot is a *mycetoma* i.e. a deep fistulous mycosis of the foot, caused by fungi which produce extra-ordinary enlargement of the affected part with abscesses osteitis and deep sinuses. In the pus coming from many fistules black or coloured grains may or may not be present.[1]

Synonyms are *Mycetoma pedis Padelkama*, *Fungus foot of India* and *Maduromycosis* (after the town Madura India).

## EPIDEMIOLOGY

It is common in some parts of Africa India Ceylon and Borneo it is seen in the West Indies Central America and Philippine Islands, although not frequently Very few cases have been reported in North America and in Europe Most of the cases are found among tillers of the soil and people who work in the fields and go barefoot BOCARRO stated that usually a thorn-prick opens the skin to the causal organism.

## AETIOLOGY

Madura foot is produced by fungi which may be found in the pus from the abscesses and sinuses, in the form of coloured grains. The size of

[1] *Paramycetoma* is an obsolete term for a deep fistulous mycosis, not producing granules

these grains is variable from one to a few millimeters in diameter they are soft and formed by the aggregation of great masses of mycelia and of some spores The fungus grows readily in adequate culture media. The colour of the grains may be black, yellow or red, and usually grains of one colour are found in each case. Classification has been attempted on the basis of the colour of the grains, but, according to GAMMEL, this is unscientific, for the same colour may be produced by various genera of fungi The fungi of Madura foot belong to the



902. Madura foot due to a fungus similar t Madurella mycetomi and producing black grains.
(Sagher–Jerusalem)



903. Madura foot.
(Sagher–Jerusalem)

Actinomyces, Madurella, Indiella, Glenospora and Monosporium among the imperfect fungi and to the Allescheria, Aspergillus, Sterigmatocystis and Penicillium among the Ascomycetes. Most of the cases of the yellow variety are produced by Actinomyces In Cuba the A. madurae was identified in one case and A bovis in another

1 Class. Schizomycetes.

A. Genus Actinomyces (NOCARDIA).

1 – Actinomyces bovis HARZ 1877

2. A. madurae BOYD and CRUTCHFIELD 1921

3 – A. asteroides (Eppinger) Gasperini 1894
4 – A. bahiensis (Piraja da Silva) Brumpt 1927
5 – A. convolutus Brumpt 1927
6. – A. indicus Kanthack, 1892.
7 – A. madurae (Vincent) Lachner Sandoval, 1898.
8 – A. somaliensis Brumpt 1927
9 – A. sp. Yazbek, 1920 (related to A. somaliensis)
10 – A. sp. Yazbek, 1920 (related to A. asteroides)
11 – A. pelletieri (Laveran) Brumpt 1927
12. – A. verrucosus (Miescher) Alder, 1934
13 – A. Ponceti (Verdun) Brumpt 1927

II Class. Fungi Imperfecti.

A. Genus Madurella

1 – Madurella mycetomi (Laveran) Brumpt 1905
2. – M. bovoi Brumpt 1910.
3 – M. oswaldoi Parreiras Horta 1919
4 – M. ramiroi Piraja da Silva, 1919
5 – M. tabarkae Blanc and Brun, 1919
6. – M. tozeuri (Nicolle and Pinoy) Pinoy 1912.
7 – M. americana Gammel, 1926.
8. – M. Ikedai Gammel, 1927
9 – M. Lackawanna Hanan and Zurett 1938.

B. Genus Indiella.

1 – Indiella mansoni Brumpt 1906
2. – Indiella reynieri Brumpt 1906
3 – Indiella brumpti Piraja da Silva 1922.

C. Genus Glenospora.

1 – G. khartoumensis Chalmers and Archibald, 1916
2. – G. semoni Chalmers and Archibald, 1917

D. Genus Monosporium.

1 – Monosporium apiospermum Saccardo 1911
2 – Monosporium sclerotiale Pepere, 1914

E. Genus Cephalosporium.

1 – Cephalosporium recifei Leao and Lobo 1934
2 – Cephalosporium sp. Carrion 1940

III Class Ascomycetes.

A Genus Allescheria.

1 – Allescheria boydii Shear, 1921

B Genus Aspergillus.

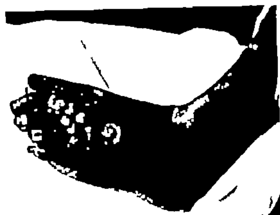
1 – Aspergillus bouffardi Brumpt 1906

C Genus Sterigmatocystis.

1 – Sterigmatocystis nidulans var. Nicollei Pinoy 1906

D Penicillium

1 – Penicillium mycetogenum Mantelli and Negri 1915.



904 Madura foot in Surinam.
*(S[illegible]–Amsterdam)*



905 Mycetoma pedis et cruris by Nocardia mexicana.
*(G. Ochoa–Mexico City)*



906. Mycetoma of the knee.
*(Oscar G. Costa–Belo Horizonte)*

**SYMPTOMATOLOGY**

In most cases the foot is the affected part and in some the hand or the knee.

Probably the organism gains access to the tissues through an injury of the skin. The disease progresses very slowly and in weeks or months a swelling of the affected part is noticeable, with the development of small, firm nodules. Many other lesions like the first begin to appear around it, and with the passage of time, the part offers a typical lumpy appearance.

Some of the nodules remain firm, a few of them develop fibrosis, but the largest number undergo central necrosis and become perforat-



907 Mycetoma of the knee
*(Orr G Coste-Bele Herrenkt)*

ed by threadlike sinuses, which exude abundant sero-pus containing the grains. These sinuses extend deeply into the tissues.

As the disease progresses, the bones and joints of the affected part develop a process of chronic osteoperiostitis and arthritis, which may cause destruction of the bones, with elimination of sequestra through the sinuses. The extent of these bone lesions may be diagnosed by roentgenograms. They often end in ankyloses and deformities.

Muscular atrophy supervenes as a sequel to the immobilization of the part produced by these ankyloses, and pain accompanies any movement.

The enlargement of the affected part becomes permanent, and very marked oedema is the rule. As a result of this, the arch of the foot is



908 Madura foot micro-abscess surrounding the grains.

909 Actinomyces from Madura foot.

not visible, the toes seem to be shortened, immovable, and more separated one from the other Around the opening of the sinuses, strawberry-like formations and irregularities appear

The disease never spreads to other parts of the body and follows a chronic course over a period of years when untreated It does not tend to spontaneous cure.

**PATHOLOGY**

The different types of parasites produce similar alterations In late cases almost always the bones, tendons, and muscles are affected, and even may be entirely destroyed.

In the pus there are numerous grains, which sometimes are so grouped as to constitute large sized bodies. Most of the nodules show a process of central necrosis

Microscopically the tissue shows a chronic granulomatous infiltration, numerous micro-abscesses and collections of giant cells surrounding the grains included in the tissue. Plasma cells are numerous at the periphery of the active lesions. In places where healing has taken place fibrous tissue may be the prominent feature, the result of scar formation.

The sections stained with haematoxylin-eosin are satisfactory in most cases For the better demonstration of the grains in the tissues, Gram should be preferred

The differential diagnosis with other similar conditions such as sporotrichosis and even with tuberculosis may be difficult in the absence of the typical grains In early cases of Madura foot.

**DIAGNOSIS**

The clinical picture is typical with usually one foot swollen and oedematous up to two or three times its normal size with a typical lumpy appearance Palpation allows the observer to define many marble sized nodules The skin and the underlying structures are criss-crossed by sinuses from which oozes a sero-purulent fluid in which the typical grains are a prominent feature.

These grains are made up of mycelium and can be identified by direct examination under the microscope in fresh preparations. Small accumulations of pus sometimes resemble these grains but they lack the radiating features of the fungous grains

Direct examination is performed by first breaking up the grains under light mechanical pressure, then placing them on a slide in a drop of 40 % potassium hydroxide solution[1] A cover slide is then lightly pressed on and the specimen is ready for examination. The microscope will reveal a profuse central mycelium and some spores in the periphery

Cultures may be grown in glucose, serum, agar or SABOURAUD's medium, but PETRAGNANI's medium, modified with asparagin, has proven in Cuba, to be most appropriate for the first culture.

Some cases have to be differentiated from tuberculosis yaws glanders, and syphilis the auxiliary laboratory methods and X ray examination being valuable for this purpose.

#### THERAPY

Although the disease is not fatal, the prognosis is not good. As a rule, only the amputation of the affected part will cure the disease, although cases have improved or been reported cured with arsphenamine and intravenous injections of mercurochrome.

Tartrate of antimony and potassium, LUGOL's solution, potassium iodide, and copper sulfate, have been used with variable results The sulfa drugs clear up the secondary infection, but have little effect on the disease. Penicillin is today the treatment of choice.

When medical treatment fails, one must resort to amputation.

[1] A modern clearing fluid is chlorallactophenol.

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CHAPTER 82

# RHINOSPORIDIOSIS

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## DEFINITION

Rhinosporidiosis is a fungous infection generally observed in the mucous membrane of the nostrils of man and domestic animals. It is characterized by the formation of irregular polypoid granulomatous growths which may be pedunculated or sessile and in which the fungus is found

## AETIOLOGY

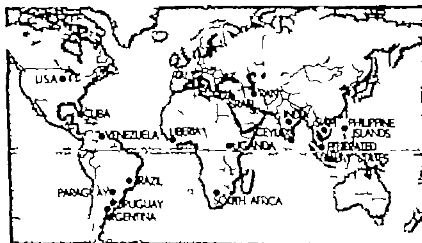
The aetiological agent is *Rhinosporidium seeberi* (WERNICKE, 1900 in Belou 1903), SEEBER 1912, emend ASHWORTH 1923

The fungus was seen in nasal polypi of man by MALBRAN, in 1892 in Argentina, by O KINEALY in 1894 in India, by SEEBER, in 1896 in Argentina, and by ELLET in 1897 in the United States of America

In 1900 SEEBER first described the fungus which he regarded a protozoon. He named it *Coccidium* In 1903 O KINEALY described his findings. MINCHIN and FANTHAM, in 1905 using O'KINEALY's material, introduced the term *Rhinosporidium* with the species *R. kinealyi* for the parasite which they classified among the protozoa. THEILER, in 1906 found the first case of rhinosporidiosis in domestic animals, in South Africa With the material of that case ZSCHOKKE described a new species *R. equi* SEEBER in 1912, established the identity of *R kinealyi* and *R. seeberi* This last name was proposed by SEEBER using the generic name *Rhinosporidium* of MINCHIN and FANTHAM and the specific one *seeberi* proposed by WERNICKE, in 1900 The vegetal nature of *R. seeberi* was definitely demonstrated by ASHWORTH who classified the parasite among the *Phycomycetes* suborder

[1] Photograph taken by FONTES and CARVALHO FILHO Rio de Janeiro

*Chytridineae* In that classical paper published in 1923 the life-cycle of the fungus in the tissues was described in detail. In 1936, CIFERRI, REDAELLI and SCATIZZI established the identity of *R. seeberi* and *R. equi*. This identity had been suspected by HARTMANN and SCHILLING since 1917 and admitted by ASHWORTH. The systematic position of *R. seeberi* among the fungi has been a matter of controversy. It is generally placed among the fungi which cause the so-called blastomycoses (ALMEIDA, CONANT *et al.*, FONSECA FILHO, GOUGEROT, NIÑO, REDAELLI, ROCHA LIMA). CIFERRI suggests that it should be classified among the *Phycomycetes* suborder *Chytridineae* in the family *Rhinosporidiaceae* with only one genus *Rhinosporidium*. Later the same CIFERRI with REDAELLI put it in the order *Chytridiales* family *Coccidioidaceae*. In reviewing the question we concluded that the systematic position of *R. seeberi* is the following: Division *Eumycetes* class *Phycomycetes* order *Chytridiales* family *Coccidioidaceae* (*sensu* REDAELLI and CIFERRI).




910. Geographic distribution of Rhinosporidiosis.

## EPIDEMIOLOGY

Rhinosporidial granuloma has been found in many countries. Most of the cases, however, were observed in India and in Ceylon where the disease is apparently endemic. Table 1 summarizes the records found in the literature up to the present. (Table 1 and Map Fig. 910).

## INCIDENCE BY SPECIES, RACE, SEX, AGE AND OCCUPATION

Most of the cases of rhinosporidiosis have been observed in man (Table 1). Among domestic animals the disease has been recorded in horses, mules and cattle.

The incidence is apparently higher among the natives of India and

TABLE 1
GEOGRAPHIC DISTRIBUTION OF RHINOSPORIDIOSIS

| Countries | Number of Cases | |
|---|---|---|
| | Human | Animal |
| AFRICA | | |
| Liberia | 1 | — |
| South Africa | 10 | 3 |
| Uganda | 2 | — |
| Total | (13) | (3) |
| AMERICA | | |
| Argentina | 17 | 11 |
| Brazil | 13 | 5 |
| Cuba | 1 | — |
| Paraguay | 10 | — |
| U S of America | 19 | — |
| Uruguay | 2 | 5 |
| Venezuela | 1 | — |
| Total | (63) | (21) |
| ASIA | | |
| Ceylon | 108 | — |
| Fed. Malay States | 1 | — |
| India | 236 | 25 |
| Iran | 35 | — |
| Israel | 1 | — |
| Siam | 2 | — |
| Doubtful | 1 | — |
| Total | (384) | (25) |
| EUROPA | | |
| Italy | 2 | — |
| Total | (2) | — |
| OCEANIA | | |
| Philippine Island | 1 | — |
| Total | (1) | — |
| Total | (463) | (49) |

Ceylon but it seems that race has no influence on the incidence, because the disease has also been observed in persons from many other countries. The environmental conditions in the geographic areas where the infection is observed seem to be of utmost importance (FAVONS FONSECA FILHO)

Rhinosporidial infection is met more often in males than in females

For many years the disease was considered peculiar to males until TIRUMURTI and DENTI observed the first cases in women, in 1922.

It seems that the disease is more frequent in young persons but the age range is very wide. It has been observed in persons from 6 to 82 years old (KARUNARATNE, MIGONE).

Occupation appears to be important as a predisposing factor. Farmers or persons who live in the country are the most affected. It is well known that mycoses, mainly the deep mycoses, chiefly occur among agricultural workers or farmers (HENRICI). ELLIS considers rhinosporidiosis as an occupational disease for agricultural workers. Divers and sandworkers (MANDLIK, NORONHA) are also infected.

In the paper by KARUNARATNE, which summarizes the greatest number of cases observed by one author, all possible data on the incidence of the disease in his 104 cases are presented.

## MYCOLOGY

*R. seeberi* has not been cultivated up to the present, only its morphological characteristics as seen in the affected tissues can be described and these were detailed by ASHWORTH. We shall summarize the life cycle.

*The early phase* is represented by a round corpuscle 2—10 μ in diameter with a thin wall membrane; this early phase was first described by SHREWSBURY. In next phase a larger organism is observed, about 12 μ in diameter, showing a double wall membrane and differentiated nucleus and cytoplasm. From this stage the fungus evolves more and more towards a round organism ranging from 50 to 60 μ in diameter; the cytoplasm is crowded with lipidic storage material.

Then begins *the nuclear division* which has been very well described by ASHWORTH. The cytoplasm divides after many nuclear divisions and is arranged around the nuclei; this division occurs when there are about 2000 nuclei. At this time the cell is still spherical having a diameter of 150 μ or more.

While the mitoses are occurring a definite thickening of the wall membrane is observable at one point. The centre of this thickening shows an opening which is called the pore.

After the organism has reached its *maximum development* it has a nearly spherical shape and measures 300—350 μ in diameter. The wall membrane is double; the outer membrane is chitinous and the inner one is of cellulose; this latter thickens appreciably (about 15 μ) in the region where the pore is observed (Fig. 911). Sometimes one can see a sort of lid closing the pore (MELLO) (Fig. 912).

The large sphere entirely filled with small corpuscles is called *the sporangium.* The small corpuscles are the spores and are very numerous, about 16 000—20,000 in each sporangium. The spores measure 7—9 μ in diameter. They show a differentiated nucleus and storage material arranged as spherules (about 10—16 spherules for each spore) (Figs. 913–915).

When *the sporangium* is completely mature, *i.e.*, when it has reached its maximum size, the spores escape slowly from it through the pore (Fig 916). If the surrounding pressure is greater the wall membrane ruptures. The spores are found scattered in the neighbouring tissues. Usually it seems that the spores are thrown into the open cavities where the growths are localized The process of liberation of the spores through the pore when the sporangium is mature is due to osmotic tension differences (MELLO)

The spores within the sporangium do not all show the same degree of development. The more developed are around the pore at the opposite pole they are flattened and little differentiated (Fig 917)

After the spores are discharged into the tissues surrounding the granuloma they evolve towards the early phase of the fungi beginning a new cycle the storage spherules disappear

## SYMPTOMATOLOGY

The nostrils are the most common sites of rhinosporidiosis, hence the generic name of the fungus. In domestic animals all the observed cases, except one with laryngeal localization (WOLFFLÜGEL), were found in the nostrils (Fig 922).

After the nose the ocular apparatus (mucous membrane of the eye and lachrymal sac) is the most affected site A few cases have been observed in the upper respiratory tract (uvula, pharynx, faucial pillars tonsils larynx, and the alae nasi)

In 1907 only two years after the genus was created, BEATTIE described one case of rhinosporidiosis outside the nose in the external auditory meatus. A few years later several cases of penile localization were observed exhibiting exceptional severity of the disease (TIRUMURTI) Cutaneous localizations were also reported (FORSYTH)

General infiltrates have been observed (ALLEN and DAVE DHAYAGUDE).

The patients showed the polypi in many parts of the body surface, sometimes very large and always with the fungus in the granulomatous tissue

*The symptoms* of rhinosporidiosis are variable according to the site of infection there is, however always the presence of polypi where *the fungus is found. In the paper by* ALLEN and DAVE one may find good descriptions of the various aspects of the human disease

Subjective symptoms are useful for the establishment of early diagnosis When the tumours are localized in the nostrils the patient feels a local indolent pruritus.

A discrete watery mucous discharge follows the amount of fluid is more abundant after a few days. If the nasal mucous membrane is examined one can see the polypoidal growths as friable, reddish, soft and with irregular surface they bleed easily when touched. At an early phase they are very small, pinpoint in size after a variable period of evolution of the disease they grow to a large size and may occupy all the extension of the septum nasi invading the neighbouring regions. At first the polypi are sessile but after development they are often pedunculated. They may be observed in one or in both nostrils and are more common in the anterior part of the nasal septum. Some times they show a roughened cauliflower-like surface.

When the tumour reaches a large size it causes the obstruction of the nostrils, and a more or less intense dyspnoea may result forced passage of the air (exercise, coughing, sneezing) may lead to epistaxis. Sometimes a secondary bacterial infection occurs and the nasal discharge becomes muco-purulent.

When the polypi are carefully examined they show on the rough or lobulated surface small yellowish or greyish dots visible to the naked eye each dot measures 0.2—0.5 millimeter and represents the adult form of *R. seeberi* surrounded by a thin layer of epithelial tissue the larger dots are micro-abscesses in the sites where the fungus is or was present.

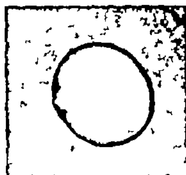
A small fragment of the growth compressed between the fingers is easily crushed and the more developed forms of the fungus give the *sensation of sand to the touch.*

During any stage of the infection the nasal discharge in microscopic examination shows the free spores or other forms of the fungus.

The general condition of the patient is not impaired unless the dyspnoea is very intense. Lymphatic nodes are not affected.

When the infection is localized in the pharynx or in the larynx the growths may lead to more or less intense dyspnoea or dysphagia according to their size.

The symptoms of *ocular rhinosporidiosis* vary with the site of the infection. The small conjunctival polypi are not usually perceptible, when they are larger however they cause the same symptoms as foreign bodies, *e.g.*, photophobia, lachrymation and conjunctival congestion. When the growth enlarges it may be sessile and sometimes

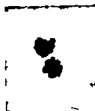


911 Developed sporangium showing the region of the pore Hematoxylineosine



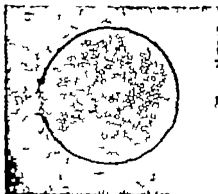
912. Part of a sporangium showing the lid closing the pore (a), spores (b), and the thickening of the cellulosic layer near the pore (c) Material fixed in Fleming's fluid.







913-915 Mature spores from a crushed ripe sporangium showing double wall membrane and spherules of storage material. Giemsa



916. M  re spores escaping from the sporan m th ugh the pore into the  nnect  tissue



917 Rupt ed sporangi m showing little differentiated spores t the pole pposite to the pore

it is observed as a polypoidal sheet between the bulbar and the palpebral conjunctiva. Cases occur in which the size of the growth is so large that ectropion results

The polypi may be localized in the lachrymal sac or obstruct the lachrymal duct in these cases abundant lachrymation or a purulent dacryocystitis may be observed.

In every case of ocular rhinosporidiosis the spores or other forms of the fungus are found in the tears on microscopic examination.

*Cutaneous* lesions are at first painless unless localized in sites subject to pressure like the soles. Later they are uncomfortable and even painful owing to their size and weight. The cutaneous polypi begin as small sessile papillomas not much raised above the skin surface during the evolution of the disease they may become pedunculated.

The lesions in the *aural meatus* are without particular characteristics the growths determine a narrowing or obstructing of the duct when they are large.

*In the penis* the lesions resemble at first venereal warts when localized on the glans later they are polypoidal and cauliflower like. When penile lesions are very large amputation of the organ becomes necessary (TIRUMURTI) In one case of DHAYAGUDE there was an urethral pedunculated tumour which could be seen only during micturition.

## EVOLUTION AND DURATION

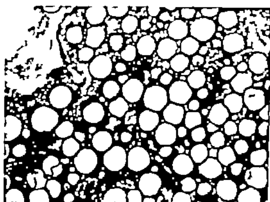
Rhinosporidiosis has a prolonged and slow evolution sometimes it evolves during many years without causing much trouble. In some cases spontaneous regression of the lesions has been observed. In general, however, there is a great tendency to recurrence after removal of the growths.

The duration is in general prolonged for many years a case of 35 years duration has been observed.

## SOURCES OF INFECTION

Since *R. seeberi* has not been cultivated as yet and even experimental infection has not been obtained, the sources of infection and the pathogenesis are unknown.

Two main hypotheses have been suggested with respect to the



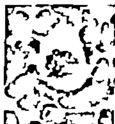
918 Section of a polypus showing at the upper left free spores of *R. seeberi* adherent to the mucus.



919 Lobulated aspect of a rhino-sporidial polypus.



920. Section of a rhinosporidial polypus showing at the upper right an isolated mass of various forms of the fungus near the epithelial surface



921 Free mature spores among erythrocytes in haemorrhagic nasal discharge. Giemsa.

source of infection direct transmission, and a life-cycle with a saprophytic phase.

In the first case, the spores of the fungus would pass directly from the lesions to other parts of the body or to healthy persons through clothes (TIRUMURTI), fingers and nails (FORSYTH, KARUNARATNE, TIRUMURTI), dust (ALLEN and DAVE, NORONHA, RAO), water (ALLEN and DAVE, MANDLIK, NORONHA, RAO), etc. Some authors suggest the existence of animal carriers (cycle in an intermediary animal host) this is contradicted by TIRUMURTI and others. CASTELLANI and CHALMERS thought that some unknown animal could be the source of the fungus. Even the possibility of existence of the disease primarily in fishes was suggested (ALLEN and DAVE), man and domestic animals being only accidental hosts.

The existence of a life-cycle with both a saprophytic and an infectious phase would exclude the possibility of direct transmission. This hypothesis shows similarities with those that have been suggested to explain the aetiology of mycoses in general (EMMONS HENRICI) some of them experimentally demonstrated like coccidioidomycosis, chromoblastomycosis, histoplasmosis, and cryptococcosis among the blastomycoses (CONANT EMMONS, STEWART and MEYER)

Whether the infective spores come from the polypi or from a saprophytic evolutive phase, the site where man and domestic animals are infected is unknown. The extensive work conducted in India suggests as predisposing causes of infection repeated contact with water and dust, possibly contaminated with the spores. It is probable that a lifecycle does exist in nature similar to that observed in other members of the order *Chytridiales* In this case the saprophytic phase would take place carried in water

#### PATHOGENESIS

The exact pathogenesis of rhinosporidiosis is as yet unknown. Many authors think that the infection of areas near primitive lesion is made by auto-inoculation, e.g. by the fingers and nails (FORSYTH, INGRAM, KARUNARATNE, TIRUMURTI, WRIGHT).

In that case lesion of the epithelium of the nostrils or of the other sites would be necessary precursor (RAO).

Dissemination through the lymphatic route would explain the appearance of lesions near others already existent more satisfactory than would auto-inoculation (DE ... AGUDE, PARODI, TIRUMURTI).

SEEBER thought that the fungus only profitted of a pre-existent granulomatous lesion to establish itself and to develop.

CORDERO and VOGELSANG having observed in a horse the presence of *R. seeberi* spores in gland ducts and mucous membrane of the nose, admitted that an inverse route could well occur, i.e. an infectious form in contact with the mucous membrane could reach a gland duct and infect deeper parts of the sub-mucous connective tissue.

A haematogenous route may explain some cases in which a generalization of lesions to various parts of the body was observed.

CASTELLANI and CHALMERS, in 1913, admitted that such infections could be found endangering the life of the patient, and in 1919 they admitted also that *R. seeberi* could give rise to a septicemia. ALESSANDRINI saw for the first time a rhinosporidial infection in which a haematogenous route could be traced: the patient had a brain tumour and a history of an indeterminate nasal infection; a large number of spores and other forms of development of the fungus were found in the fluid of the tumour. RUIZ and OCANA observed spores of the fungus in the lumen of nasal blood vessels; this fact is of some importance as evidence that dissemination by haematogenous route may actually occur possibly leading to metastasis as in the cases of ALESSANDRINI, ALLEN and DAVE and DHAYAGUDE.

## HISTOLOGY

The principal feature of a histological preparation of rhinosporidial polypus is the presence of *R. seeberi* in various stages of development (Fig. 918).

The paper by KARUNARATNE based on the observation of 34 cases, as well as that of ASHWORTH, gives excellent descriptions of the histopathology of the disease. A general feature is the slight inflammatory reaction in the affected tissues and the lack of involvement of neighbouring tissues such as the size of the tumour would suggest.

When one examines the histological sections with low power magnification the irregular contour of the polypi is seen formed by epithelial growth (Fig. 919).

If the polypi are localized in the anterior part of the nostrils the epithelium is stratified squamous but in the posterior parts it is simple columnar or perhaps ciliated. From many sites of the inner surface of the epithelium crypts may grow deep in the polypus. In other instances the epithelium is very thick in certain places and thin in others, specially in those where a ripe sporangium is situated.

In the external surface of the epithelium many spores and fully developed sporangia are observed adherent to the mucosa.

The presence of *R. seeberi* in the epithelial layer is not very common. The sporangia which are near this layer compress the cells and sometimes these are completely separated and the pore of the ripe sporangium is turned to the surface of the growth. In other cases a sort of nest of various forms of the fungus is found almost isolated from the main part of the polypus (Fig. 920).

A great part of the granuloma is formed by oedematous connective stroma with many blood vessels and infiltrated plasma cells, polymorphonuclear neutrophils and histiocytes; eosinophilic cells are abundant in some cases but rare in most. Areas of recent haemorrhage are observed in many sites; in other parts of the section haematogenous pigment granules are observed indicating previous haemorrhages.

The smaller forms of the fungus may be seen inside the connective tissue cells. The ripe sporangia are seen ruptured or discharging their spores through the pore (Fig. 916, 917); these may be localized at the surface of the epithelium and in this case the spores are thrown outside the growth or in the lumen of a gland duct (CORDERO and VOGELSANG) or a blood vessel (RUIZ and OCAÑA). It is more frequent, however, for the sporangium to open in the connective tissue and the spores and early forms of the fungus are found among the connective tissue cells.

Tissue reactions of various types may be found owing to the presence of the fungus in the tissues, such as micro-abscesses, giant cells, reticular hyperplasia and telangiectases.

When the sporangium sheds its contents into the connective tissue through the pore or after the rupturing of the membrane, a leukocytic infiltration is seen beginning in the pore or at the site where the wall membrane is ruptured. If the amount of leukocytic cells is great, micro-abscesses are formed and sometimes the sporangium remains completely empty surrounded by pyocytes. This type of lesion was observed with much frequency in NORONHA's cases.

A thorough examination of the section may detect giant cells of Langhans type; they are more common around the ruptured sporangia and may be seen inside them. These giant cells may also surround normal spores or those which are disintegrating.

The reticulum increases greatly and forms a sort of basket or nest, according to TATO and MOTTO, surrounding the fungus. FIALHO believes that the enlargement of the fungus during its life-cycle leads to the compression of the argyrophilic fibres and when the sporangium is fully developed the reticular structure appears as membrane when it is observed after the common staining procedures.

The fragments of sporangia may be seen inside giant cells or scattered among the connective tissue cells. Most of them have the membrane collapsed or looped back by virtue of its elastic character. Sometimes the surrounding tissues or leukocytic infiltration may invade the interior of the sporangium which is otherwise apparently normal. ASHWORTH and BEATTIE illustrated this fact and believed that such invasion took place through the pore but other hypotheses may be possible (KARUNARATNE).

The histopathological study of rhinosporidial granulomas has led some workers to observe at the same time pathological changes indicating other diseases such as squamous carcinoma (KARUNARATNE), leishmaniasis (MIGONE) and leprosy (ALLEN and DAVE, ROSENBAUM).

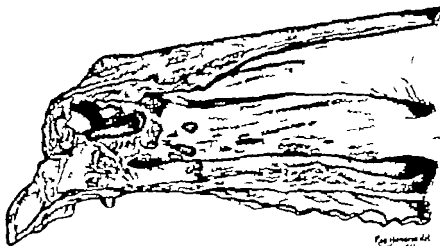
ROSENBAUM, in Israel, described a case of human rhinosporidiosis associated

with leprosy in which cells very similar to those of Mikulicz of rhinoscleroma were observed.

## DIAGNOSIS

The diagnosis of rhinosporodiosis is easy because of its symptomatology and the microscopic appearance of fragments of the tumour. A small portion of the growth can be examined between slide and cover slip mounted in any suitable fluid used in mycological examination of scales or even in water All the forms of the life-cycle of the fungus may be seen.

The microscopic examination of nasal and ocular discharge may



922 Rhinosporidial polypi in the nostril of a horse

reveal the spores or other forms of the parasite (Fig 921). When one is confronted with a case of nasal tumour or habitual nasal discharge or epistaxis one should think of rhinosporidiosis.

The presence of small yellowish or greyish dots on the surface of the growth may be considered characteristic of the rhinosporidial polypi.

The differential diagnosis must be made to exclude the following hypertrophic rhinitis allergic mucous polypi syphilitic condylomas, angiofibromas vascular polypi of the nasal septum, angiomas, nasal and nasopharyngeal fibromas papillomas, sarcomas, epitheliomas leishmaniasis (mainly in its granulomatous secondary stage), tuberculosis leprosy rhinoscleroma and blastomycoses

## PROGNOSIS

The prognosis of rhinosporidiosis is variable but in general it is benign. In most cases the disease evolves gradually and is not disseminated. When the lesions are very extensive or disseminated a bad prognosis is warranted owing to intense dyspnoea or dysphagia, or other secondary manifestations.

In some cases spontaneous regression of the lesions may be observed (ALLEN and DAVE, FORSYTH, SEALE *et al.*) Other cases are serious owing to the situation of the growths (ALESSANDRINI, ALLEN and DAVE, ELLES, TIRUMURTI).

## THERAPY

Rhinosporidiosis has been treated with many drugs without good results. Surgical treatment seems to be best.

The authors who worked in India have the largest experience with drugs. They used instillations of 2 per cent. tartar emetic solution three times a day (WRIGHT), neostibosan, sulphostab, casbis, entodan, fouadin, *para*nitrophenol and urea stibamine (ALLEN and DAVE), 5 per cent. tartar emetic solution, chlorohydroxyquinoline ointment (REICHMANN) etc. Some of these seemed to give good results but most of them failed to cure the disease

*Surgical removal of the growth is indicated.* A large portion of the apparently normal tissues which surround the polypi must be removed in order to avoid recurrences which are very common. When the tumours are pedunculated surgery gives good results, but when they are sessile and very extensive recurrence is the rule.

The use of a simple snare seems to contribute to the dissemination of infectious forms of the fungus to the neighbouring tissues it is better to use a galvanocautery

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CHAPTER 83

# ASPERGILLOSIS

ANDREW G. FRANKS – New York
ALVO GUIDUCCI – New York

Aspergillosis caused by one or more species of Aspergillus, is an uncommon and ill-defined disorder primarily affecting the bronchi and lungs or the internal auditory canal, and occasionally involving the skin, nails, nasal sinuses orbit, bone and meninges.

## EPIDEMIOLOGY

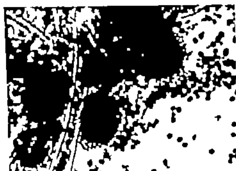
The Aspergilli are regular inhabitants of the soil and are believed to be widespread in nature. Although over 350 different species have been collected in all parts of the world, they are commoner in warm, damp climates. Many species are pathogenic for plants. Birds, especially pigeons and parrots are particularly susceptible, but some species infect insects and domestic animals, and also presumably man.

Since the Aspergilli are so ubiquitous and are very frequently encountered as saprophytes in routine laboratory cultures the role that they play in initiating or perpetuating pathological lesions in man is still debatable. Nevertheless the ever increasing case reports of human Aspergillosis would seem to indicate that, occasionally these organisms can be pathogenic for man. Aspergillus fumigatus is the species most commonly isolated from diseased human tissue and is believed to be pathogenic; however available data have shown that on occasion, Aspergillus niger, Aspergillus glaucus and Aspergillus nidulans may be the offending organisms. It is believed that pigeons, parrots and other birds may constitute the medium of exposure. Pulmonary in-

fections are found chiefly in wigmakers who use cornmeal for freeing hair from oil, in fur cleaners who use rye flour, containing the spores, as a grease remover in pigeon feeders who chew grain which they then force with their own mouth into the beaks of squabs in order to fatten them, and in agricultural workers who are continuously exposed to the dust from threshers Repeated and prolonged exposure to the organism seems necessary for the development of the disease.

## SYMPTOMATOLOGY

The symptoms of Aspergillosis vary with the location of the infection. A) *Aural Involvement* – Infection of the external auditory canal Otomy-



923 A culture mount of Aspergillus niger

cosis) is publicized as the commonest manifestation of Aspergillosis, but the organism may solely live in the cerumen as a saprophyte. In certain parts of the world, especially China, where this type is supposedly very common, it has been given the special name of 'Hong kong ear It manifests itself in this location as a scaly dermatitis covered with a thick, firm greenish cerumen.

B) *Pulmonary Aspergillosis* – Involvement of the bronchi and lungs is probably the most important clinical manifestation of Aspergillosis. The disease may be acute or chronic. In the former it may resemble a severe bronchopneumonia with fever, cough, hemoptysis, dyspnea, and expectoration of a green or greenish-black mucopurulent sputum. Pathologically the bronchi are filled with pus and the mucosa is red and swollen There is a purulent inflammation on the pleura, and numerous, small white nodules are found scattered throughout the parenchyma of the lungs. In the chronic form, it simulates very closely pulmonary tuberculosis with an insidious onset and course Here there is increasing cough, a remittent fever a slow

steady weight loss and gradual emaciation. Pathologically tubercle-like structures are found, and in the severe forms, cavitation occurs. Pulmonary aspergillosis is very difficult to diagnose prior to necropsy At autopsy it may be found disseminated in nearly all of the organs of the body

C) *Nasal and Maxillary Sinus Aspergillosis* – The clinical appearance is characterized by a chronic, periodic discharge of pieces of a greenish, gelatinous, membranous material in which the organism can be demonstrated. Extension from the maxillary sinus may involve the orbit.

D) *Nail Involvement* – Numerous cases of onychomycosis have been reported, which clinically show thickening, brittleness, greenish or yellow discoloration and crumbling of the distal portions of the nails




924 X ray of a case of pulmonary aspergillosis. Before and after iodide therapy

*(Peterson–New York)*

E) *Miscellaneous* – Granulomatous lesions of the skin have been recorded which are not diagnostic clinically Aspergilli have been isolated in cases of maduromycosis Especially in these forms, however the presence of the organism on culture may only signify a secondary non pathogenic invasion

Cases are on record in which the Aspergillus has caused meningeal infections involvement of bone especially the ribs and vertebrae with formation of sequestra bathed in pus dacrocystitis and blepharitis and genital lesions

DIRECT EXAMINATION

Special care must be taken in obtaining any material for direct exami-

nation. In collected sputum which is pressed to a thin film under a coverglass one sees broken fragments of hyphae with numerous, small, round, dark green spores measuring 2–3 microns in diameter In microscopic sections of diseased tissue, one finds a similar picture of mycelial elements with numerous, small round spores.

## CULTURE

Aspergilli are fast-growing fungi Inoculated on Sabouraud's medium and incubated at room temperature, it first appears as a white, filamentous growth on the surface of the medium, but quickly becomes green or greenish-black as spores are produced. The organism needs adequate oxygen tension for the development of fruiting heads, although mycelia proliferate under relatively anaerobic conditions. Since it is a common contaminant and a fast-grower, it may hinder or inhibit the growth of a slower growing pathogenic fungus.

## MICROCULTURE

All species are composed fundamentally of a stalk with a sporebearing head. The surfaces of the enlarged vesicles at the end of the conidiophores are covered with sterigmata bearing long chains of spores. The flask-shaped sporebearing of fruiting heads can be best seen by examining the culture under the low objective of the microscope. If one makes a culture mount, to which are added a few drops of lactophenol cotton blue, one sees typical swollen conidiophores with sterigmata, with long, fragile spore chains in narrow columns attached to them, or lying in close proximity

## DIAGNOSIS

A definitive diagnosis of aspergillosis is very difficult to attain, not only because of the atypical clinical manifestations, but also because isolation of the fungus does not preclude that it is the offending organism. A history of repeated exposure may be helpful. Repeated demonstration of branching hyphae and repeated cultures of the microorganisms in massive quantities and the exclusion of other possible pathogens must be obtained in order to entertain the diagnosis of aspergillosis. Aspergilli have been cultured from normal sputum, and have frequently been isolated from the sputum of patients with chronic bronchitis pulmonary carcinoma, intrinsic asthma, lung abscess

tuberculosis cavities and bronchiectasis. In other lesions one must find the organism in biopsy specimens of the tissue.

The roentgenological aspects of pulmonary aspergillosis are not diagnostic the most frequent diagnosis made by X ray is chronic tuberculosis Early in the disease, only increased lung markings are seen later there is a microflake mottling widely distributed throughout the lungs with a special disposition to exempt the apices and to concentrate in the mid lung fields and bases there may be some limitation in diaphragmatic excursion fibrous rings may appear walling off small cavities or surrouding calcareous nodules Healed cases show only increased lung markings

## THERAPY

Superficial lesions are best treated with thymol iodide or 2 per cent thymol in alcohol. Large granulomatous areas especially in cases of maduromycosis should be excised or the limb amputated. Grain threshers should wear a gauze mask as a precautionary measure, and patients with pulmonary aspergillosis who are exposed to the fungus should change their occupation or environment.

In addition to supportive therapy such as wholesome food and adequate rest saturated solution of potassium iodide is indicated if pulmonary tuberculosis is definitely excluded. Vaccines are of dubious value

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CHAPTER 84

# MUCORMYCOSIS

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ALVO GUIDUCCI – New York

## DEFINITION

Mucormycosis is an infection caused by several different strains of Mucoracea, primarily affecting the lungs or the external auditory canal, but also reportedly attacking the nose, skin, nails, and least often, the central nervous system.

## EPIDEMIOLOGY

The species of moulds which comprise the family Mucoracea, are quite numerous and widespread in nature, living as saprophytes on many plants and animals. They are very common laboratory contaminants and are often found on bread moulds.

Mucor can be pathogenic for animals spontaneous infections have been reported in dogs, birds horses, cows, and pigs. Mucormycoses of animals are of importance because, presumably they are transferable to man. The lesions produced in animal infections are quite similar in location and in histologic characteristics to those reported in human beings.

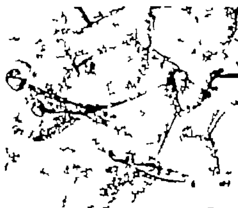
Mucormycosis can be reproduced in laboratory animals. Spores of Mucor corymbifer Mucor pusillus, Mucor rhizopodiformis, and Mucor ramosus, when injected into the blood stream of rabbits have been reported to have reproduced widespread abscesses which have resulted in the deaths of animals.

Although a number of reports of human infestation are found in the

literature, in most of these, a definite diagnosis of Mucormycosis as a primary disease, was not established. The medium of infection for man is not definitely known, but obviously overwhelming and prolonged exposure to the organism is necessary to initiate clinical and pathological lesions. It has been recorded in workers with prolonged exposure to manure and soil, and particularly in patients who have had long standing diabetes

## SYMPTOMATOLOGY

The symptoms and signs of Mucor Infection will depend upon the organ or organs involved Mucormycosis of the lungs cannot be dis-



925 Photomicrograph of culture mount of Mucor

tinguished clinically from other chronic pulmonary diseases especially tuberculosis and the other pulmonary mycotic infections A chronic cough hemoptysis expectoration of a brownish sputum and pleuritic pain may be present.

Mucormycosis of the central nervous system may become first manifested by headache, increasing drowsiness, vomiting and a confused mental state The patient may progress into a state of coma. Since invasion of the meninges and brain by this fungus is usually by way of the orbit, eye symptoms and signs are present. There may be proptosis which is usually unilateral and marked conjunctival oedema. Necrosis of the orbital tissue and osteomyelitis of the orbital bony plates may

supervene, and enucleation becomes necessary Symptoms and signs of a clear-cut meningitis may become evident. The comatose condition usually increases and the patient eventually succumbs.

Otomycosis caused by a strain of Mucor is indistinguishable clinically from that caused by other fungi The few recorded cases of mucormycosis of the glabrous skin presented dark-red, jelly-like granulomatosis lesions with a small amount of serosanguinous drainage.

Paronychia caused by this fungus, reputedly occurring in orange workers, is no different clinically from that of other aetiologies.

## DIRECT EXAMINATION

Examination of a potassium hydroxide treated specimen of material containing Mucor whether it is pus, sputum, or skin scrapings, will show abundant, coarse, non-septate mycelial elements with typical rounded sporangia at the terminal portion. The large diameter of the hyphae, the manner of branching, and the black or brown coenocytic structures are characteristic of the Mucoracea.

## CULTURE

The cultural characteristics of Mucor are quite similar to those of Rhizopus It is a fast-growing fungus filling a petri dish in four of five days. There is an abundant growth of a woolly aerial mycelia, which at first is white, but as the culture becomes older changes gradually to a dark gray The terminal portions of the mycelia are tipped with gray to black spore-heads.

## MICROCULTURE

Culture mounts of Mucor prepared with lactophenol cotton blue will reveal non-septate vegetative mycelia which gave rise to sporangiphores of equal length. These, in turn, branch irregularly and bear terminal, round spore-filled sporangia. Since the wall of the sporangium is easily broken, the elliptical spores may be found lying free When this occurs, a fragment of the sporangial wall at the base of the spherical columnella, which is the swollen end of the sporangiophore extending into the sporangium, can be seen. Although Mucor is closely related to the genus Rhizopus, it can be readily differentiated by the absence of runners or stolons, so prevalent and characteristic of Rhizopus.

## DIAGNOSIS

The diagnosis of mucormycosis should be made with extreme reluctance. The pulmonary X ray findings are reported to consist of marked exaggeration of peribronchial shadows suggestive of bronchiectasis and a ground-glass appearance in the bases associated with asbestosis. The diagnosis is one which is made in the laboratory Since Mucor is a notorious saprophyte, all other possible aetiologic organisms must be excluded before this diagnosis can be entertained. One should be able to observe the typical large mycelia in sections of diseased tissue, and one should culture the organism from tissue repeatedly and in large quantities. Even if all these criteria are fulfilled, a definitive diagnosis, although very suggestive, is, in our opinion, still open to question.

## THERAPY

The treatment for mucormycosis is the same as that for aspergillosis. Iodides in various forms for local therapy and as a saturated solution for systemic use, is the treatment of choice.

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CHAPTER 85

# PENICILLIOSIS

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ALVO GUIDUCCI – New York

## DEFINITION

Penicilliosis is the name ascribed to the condition ostensibly caused by various species of Penicillium. The few isolated reports of this nebulous condition have included pulmonary involvement, onychomycosis, otomycosis, and maduromycosis.

## EPIDEMIOLOGY

Various species of Penicillium are among the most notorious contaminants, and are present nearly always in the air and the laboratory. Because they are such common saprophytes, it is extremely difficult to establish any aetiologic relationship to pathological processes. Even their reported pathogenicity for animals other than man is not conclusively established.

Some more recent reports tend to incriminate strains of Penicillium along with other moulds as excitants capable of producing paroxysms of allergic bronchial asthma.

Species which supposedly can be pathogenic for man include P. bertai, P. mycetomogenum, and P. crustaceum. One species, P. notatum, produces the very important antibiotic, penicillin.

## SYMPTOMATOLOGY

The symptoms which may be due to infection with this organism depends on the location and organ involved. It is unnecessary to attempt to detail these symptoms here; it is sufficient to state that a case of penicilliosis has been recorded as simulating pulmonary abscess

with the symptoms and signs expected in that condition that there have been a few scattered reports of chronic, diffuse pulmonary mycotic diseases especially in grain workers which were believed to be due to Penicillium that otomycosis indistinguishable from that of other aetiologies has been attributed to Penicillium and that it had been listed as one of the many organisms capable of producing the clinical entity of maduromycosis.



926. Culture mount of Penicillium.

## DIRECT EXAMINATION

A direct examination of infected material is certainly not diagnostic. Small round spores and bits of hyphea, similar to these seen in aspergillosis are found.

## CULTURE

Penicillium is a fast growing organism. Colonies are usually white at first and then as they grow older will vary in hue, including green blue, yellow purple red and other colours The vegetative mycelium is abundant it may be colourless or secondarily coloured by metabolic products. The substratum of the culture may also be secondarily discoloured. The colony may become very powdery due to the abundant sporulation of the aerial mycelia.

## MICROCULTURE

There is no vesicle formation the conidrophores branch directly from the vegetative mycelium and may present many variations. These sterig mata may be single from which chains of spores are formed, or they may branch several times. The conidia may vary in shape from cylindric, spherical, ellipsoid, or avoid configuration and show a "broom-like" patterning

## DIAGNOSIS

To establish a diagnosis of penicilliosis is exceedingly difficult. Even when the evidence appears overwhelming, one should be hesitant in concluding that Penicillium is the offending organism. Cultures of this organism from diseased tissue do not justify labelling it a primary of fender

Nondescript pulmonary X ray findings reported included exaggerated reticular markings, peribronchial thickening and some enlarge ment of hilars peribronchial glands.

## THERAPY

The therapy presumably is the same as that given for aspergillosis or mucormycosis.

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CHAPTER 86

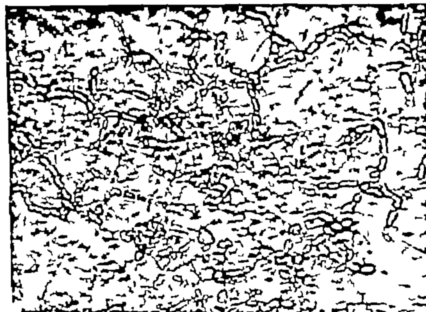
# MOSAIC FUNGUS

A. GONZALEZ OCHOA
Mexico D.F

When scales taken from a cutaneous lesion, in which a dermatophytosis is suspected, are clarified by KOH for the microscopic observation, artefacts appear to which WEIDMAN (1927) called attention and named "*mosaic fungus*" These formations which could be confused with filaments of the dermatophyton have an irregular contour and follow the borders of corneal cells, lacking septa and internal structure. The importance of these artefacts has been exaggerated, in respect to the possibility of confusion with authentic hyphae. The true filaments have a regular diameter while the mosaic fungus presents dilatations and narrowings. Another difference is that the filaments of the dermatophyton show septa, may or may not break up into arthrospores pass among the corneal cells and not only around them, and it is possible to see their cytoplasmic structure.

Formerly these artefacts were interpreted by WEIDMAN as degenerated fungous filaments but they are known to correspond to a saponified lipoid material possibly cholesterol or oleic acid (DAVIDSON and GREGORY 1935). According to DOWDING the mosaic fungus could be a fungus product Undoubtedly there exist artefacts—which may be confused with other mycotic elements and yet go unnoticed The use of chlorallactophenol d Amann to clarify the scales instead of KOH besides avoiding to a certain extent the formation of the mosaic fungus has the advantage of avoiding heating the preparation and

the material observed can be cultured free of bacterial contamination, but it cannot be left for long periods in this medium.[1])



927 Mosaic fungus (Weidman) simulating mycelia.

*(Cremer–Amsterdam)*

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1) See also page 1039

CHAPTER 87

# THERAPY OF THE MYCOSES

GEORGE M. LEWIS – New York
*DOUGLAS P. TORRE – New York*

Before treating fungous diseases of the skin a number of factors in addition to determination of the aetiological agent are often important. Among these are region of body involved depth of process possibility of coincident infection of accessory skin structures (hair nails, etc.) or of other organs (lung, bone, etc.) allergic status of the patient *to the particular fungus absence or presence of secondary pyogenic* or mycotic infection and the general medical status of the patient. When these are known, an integrated plan of treatment suited to the individual and his particular fungous disease can be instituted. Therapy may be classified under the following major topics

A Topical Medication
B Systemic Medication
C. Physical Therapy

## A. TOPICAL MEDICATION

Medications applied directly to the site of infection are the most frequently used in treatment of superficial mycoses As in the therapy of other dermatoses there are general rules to follow The type and strength of medication should be suited to the kind of disease process. The more acute and inflammatory the disorder the more bland the local medication to be used For acute inflammatory lesions with oedema, vesiculation, or exudation, wet dressings or baths are em-

ployed. As the process becomes less inflammatory lotions, pastes, paints, and tinctures may be used. Ointments are used only on chronic or dry lesions.

### B SYSTEMIC MEDICATION

Systemic medication is used chiefly in deeper mycotic infections, but also has a place in the treatment of superficial infections. It is used for

1. Fungicidal or fungistatic action. (As iodides in sporotrichosis)
2. Desensitization to a particular fungus (As in blastomycosis)
3. Treatment of secondary infection. (As sulfonamides in secondarily infected dermatophytosis)
4. Symptomatic relief (As antihistamines in any pruritic mycosis)

### C. PHYSICAL THERAPY

Physical therapy has only a limited place in the treatment of mycotic infections. Those forms used are

1. Radiotherapy
2. Heliotherapy
3. Cryotherapy
4. Surgery (including electrosurgery)

*Radiotherapy* for mycotic infections is for practical purposes limited to roentgen irradiation, although radium or its by-products could be used. The X rays have little if any true fungicidal effect. Their value depends on their action on the tissue response to fungous infection (granulation tissue, etc.), and their effect on the accessory skin organs. In tinea capitis due to *Microsporum audouini* a depilatory dose of X rays is given so that the infected hairs will be shed. In granulomatous mycoses such as actinomycosis, X rays have an effect on the granulomatous portion of the lesion while systemic medication combats the aetiological agent. In such conditions as dermatophytosis, the X rays might have a beneficial effect by retarding the sweat glands and thus eliminating the frequently contributary hyperhidrosis.

1 In this section fractional therapy means a dosage of 75 roentgen units administered at weekly intervals by a machine in the 60-100 kilovolt range. Semi-intensive therapy refers to a dosage of 150 roentgen units at two week intervals. Filters may or may not be used. Intensive therapy refers to a dosage of 300 roentgen units or more in a single dose. Higher kilovoltage may be used. Filtration with 2 or 3 mm aluminum is usual.

*Heliotherapy* in the form of ultraviolet irradiation is occasionally used in the more superficial fungous infections Beneficial action is probably indirect through desquamation of the outer layers of the skin containing the fungous elements and due to bactericidal action on secondary infection. Filtered ultraviolet rays while not fungicidal are useful diagnostically and in following progress in those mycoses with fluorescent phenomena.

*Refrigerants* in the form of ethyl chloride spray or solid carbon dioxide is of even less use than heliotherapy Like ultraviolet irradiation, refrigerants can cause a superficial desquamation.

*Use of the scalpel or electrosurgical unit* in fungous infections is limited to treatment of disorders in which topical or systemic medication is ineffective or only partially effective this includes chromoblastomycosis. This form of treatment may also be considered in potentially systemic diseases in which the diagnosis is established while the process is limited to one or a few localized areas. This applies particularly to blastomycosis.

## SUPERFICIAL MYCOSES

**Dermatophytosis** (athlete's foot, ringworm of the hands and feet, epidermophytosis trichophytosis)

*Inflammatory type or phase* In the presence of acute lesions the wet dressing listed in the formulary section (boric acid solution, aluminum acetate solution, etc.) are indicated. If secondary infection is present, antibiotics or sulfadiazine may be given concurrently Trichophytids, if present, are treated symptomatically and antihistamines are prescribed for the relief of pruritus or in the presence of allergic phenomena. As the inflammation subsides the milder liquid applications may be used

*Non-inflammatory type or phase* The ointments listed may be used, initiating therapy with the milder preparations and reserving the keratolytics for chronic lichenified lesions. In ambulatory patients it is best to apply ointments at bedtime and prescribe a powder for daytime medication.

*Prophylaxis* Daily use of a fungicidal powder

**Onychomycosis** (tinea unguium ringworm of the nails)

The fundamental principle of treatment is frequent adequate

removal of the infected portion of the nail followed by application of strong fungicides such as Whitfield s ointment, chrysarobin, anthralin, etc. Removal of the infected nail may be accomplished by scalpel, abrasives or scraping with the edge of broken glass. The program will necessarily extend over a long period of time. If only one finger nail is involved, surgical evulsion of the nail plate under procaine anaesthesia may be considered. (See also Chapters 67 and 68 )

**Tinea Corporis** (tinea circinata, ringworm of the body tinea glabrosa)

*Inflammatory type or phase* Wet dressings or baths are indicated. With subsiding of inflammation, solutions tinctures and lotions are then useful.

*Non-inflammatory type or phase* Ointments containing ammoniated mercury sulphur or the unsaturated fatty acids may be prescribed. Stronger medications such as chrysarobin and anthralin are used only on the chronic infiltrated lesions as characterized by T purpureum infections For *Majocchi's granuloma* roentgen irradiation and systemic iodide therapy may be necessary

**Tinea Cruris** (ringworm of the groin, "jockey itch")

*Inflammatory type or phase* Wet dressings are indicated initially As inflammation subsides lotions, solutions, and tinctures may be used. Since this region is readily irritated, mild medications are to be pre ferred.

*Non-inflammatory type or phase* The milder ointments usually start ing with half-strength Whitfield ointment are applied at night. Pow ders or lotions are used during the day if the patient is ambulatory

**Tinea Capitis** (ringworm of the scalp)

*Non-resistant infections* Infections caused by *Microsporum lanosum Microsporum fulvum* and the ectothrix Trichophyton group which cause an inflammatory response, can usually be cured by topical medication combined with manual epilation of the hair as it is loosen- ed by the inflammation. Salicylanilide ointment is favoured but any of the other fungicides such as sulphur or ammoniated mercury may be used successfully

*Resistant infections* Infections caused by *Microsporum audouini Tricho-phyton schoenleini* or the endothrix Trichophyton group frequently do not respond to topical medication alone X ray epilation of the hair by

the Kienbock Adamson technique is still the method of choice. This is a highly specialized procedure and should be carried out only by a dermatologist or radiologist thoroughly trained in the technique. The dose of X rays must be carefully computed and accurately and skillfully administered. Postradiation treatment is important. When the hair becomes loose on the 18th to 21st day removal should be facilitated by daily shampoo and application of an adhesive plaster cap which is left on for 24 hours The Wood s light is helpful in deter mining if and where infected hairs remain so that they may be removed manually Mild fungistatic ointments are used topically until cure is established.

## Tinea Barbae (tinea of the beard, 'barber s itch ')

*Inflammatory type or stage* Hot wet dressings of boric acid solution are used initially Vleminckx s solution as a hot wet dressing is also valuable, starting with a weak solution (2 per cent.) and gradually increasing to half strength.

*Non-inflammatory type or stage* The stronger fungicides in ointment form may be used. Manual epilation of the infected hairs is indicated. X ray epilation of the beard is rarely necessary or advisable.

## Tinea Versicolor (pityriasis versicolor chromophytosis)

Daily application of a 10 per cent. aqueous solution of sodium thiosulphate following a hot bath and scrubbing with a brush is a most effective remedy The Wood's light is helpful in determining the effectiveness of treatment and when a cure has been obtained

### Erythrasma

Treatment is identical with that of tinea versicolor

### Tinea Imbricata

This disease is resistant to treatment. Fungicidal ointments containing chrysarobin of resorcinol 25 per cent in tincture of benzoin are advocated

## Otomycosis (myringomycosis tinea of the ear canals)

This diagnosis is probably made too frequently since cultural studies are not often confirmatory and pathogenic fungi are seldom found. The most effective treatment is reliance on anti-bacterial and

symptomatic measures. Neomycin is effective against B pyocyaneus which is a frequent aetiological agent. Irrigation with hydrogen peroxide (half strength) is helpful in removing exudates and detritus from the ear canal. Gentian violet 1 per cent aqueous or silver nitrate 2 per cent aqueous may be applied. The antihistaminic drugs internally often help X ray therapy (fractional dosage) may be useful.

### Lepothrix (trichomycosis axillaris)

Shaving is simple and effective. If this is not desirable the hairs may be freed of the fungous concretions by application of xylene (10% in mineral oil)

### Tinea Nodosa (piedra)

Treatment is application of an aqueous solution of bichloride of mercury (1 2000) daily following a vigorous shampo

### Chromoblastomycosis (dermatitis verrucosa)

Systemic iodide therapy is of questionable value. Lesions must usually be removed either by electrosurgery or by scalpel surgery followed by skin grafting

## INTERMEDIATE MYCOSIS

### Moniliasis

*Localized type* (perlèche, glossitis, thrush, vaginitis, intertrigo) – The application of gentian violet is usually effective. Wet dressings of potassium permanganate 1 2000 or bichloride of mercury 1 1000 may be used. All these medications have the disadvantage of staining Benzalkonium chloride (Zephiran) 1 5000 to 1 20000 is sometimes effective and is particularly useful in the oral forms as it does not stain. Gentian violet is available in suppository form for vaginal use For the more chronic lesions ammoniated mercury ointment may be used.

*Onychia and paronychia* The medications listed above may be used. In addition, the infected nail should be pared away frequently and the use of soap and water is interdicted. Superficial X ray therapy (fractional dosage) is often beneficial in controlling the inflammatory reaction of the paronychia. Nail evulsion is usually contraindicated.

*Systemic type* The gastrointestinal type is difficult to cure. Low starch diets are helpful. Small doses of gentian violet may be given orally in capsule form. In the meningeal and haematogenous types oral iodide therapy is indicated. In the bronchopneumonic type inhalation of ethyl iodide has been recommended.

DEEP MYCOSES

**Actinomycosis** Combined therapy (penicillin, sulfadiazine, and roentgen irradiation) as advocated by LAMB and others is the present treatment of choice. Penicillin and sulfadiazine are given in full dosage and the X rays are given in semi intensive dosage with filtration to all accessible lesions. Reliance on systemic iodide therapy is no longer advisable. Recently the newer antibiotics (terramycin, chloramphenicol, and aureomycin) have been shown to be useful and stilbamidine is promising Surgical treatment of small lesions is sometimes advisable Irrigation of the sinus tracts with Lugol s solution (half strength) is helpful in some cases.

**Mycetoma** (maduromycosis) Treat as for actinomycosis.

**Nocardiosis** (actinomycosis without granules) Treat as for actinomycosis.

**Sporotrichosis** Iodide administration is still the method of choice. Semi intensive X ray therapy with filtration is also advisable. Excision of or incision into lesions is contraindicated. Fluctuant lesions may be aspirated with a sterile needle. Local treatment as for actinomycosis is sometimes beneficial. The antibiotics and stilbamidine may be tried if a resistant infection is observed.

**Blastomycosis.** Systemic iodide administration has long been the standard therapy Experimentation with stilbamidine has proved its effectiveness and while it must be given carefully (by intravenous drip) because of its toxicity stilbamidine is now the therapy of choice. Excision or electrosurgical removal of localized lesions of small size has the advantage of eliminating a focus. Semi-intensive X ray therapy is helpful as an adjunct in controlling the granulomatous element CONANT and other authors advocate desensitization of the patient to Blastomyces antigen if hypersensitivity is present on testing

**Histoplasmosis.** Treatment is usually ineffective. Benign form heals spontaneously and malignant systemic form is usually diagnosed post-mortem. MELENEY advocates trial of Fuadin (trivalent antimony) or Neostam (pentavalent antimony)

**Torulosis** (European blastomycosis, cryptococcosis)

Treatment is unsatisfactory Withdrawal of spinal fluid sometimes affords symptomatic relief Iodide administration or sulfadiazine in dosage sufficient to maintain a blood level of 8 to 12 mg per cent. may be tried. Lobectomy of a solitary pulmonary lesion affected an apparent four year cure in one case. (BERK and GERSTT *J A M A* 149 (1952) 1310

**Rhinosporidiosis.** Treatment of choice is surgical or electrosurgical removal. ALLEN and DAVE advise a course of neostibosan as an adjunct to surgery)

## FORMULARY

### A. WET DRESSINGS

This type of application combines a vehicle (water) for removing exudates and crusts with a medication having mild astringent anti fungal and anti-bacterial activity

*Mild*

1 Boric acid solution (saturated)
2 Aluminum acetate solution (Burow) 1 10 to 1 50

*Stronger*

3 Potassium permanganate solution 1 10 000 to 1 50 000
4 Silver nitrate solution 1 100 to 1 1000
5 Bichloride of mercury 1 1000
6. Vleminckx s solution 1 10 to 1 50

### B. LIQUID APPLICATIONS

These preparations are painted on and allowed to dry

*Mild*

7 Gentian violet 1 per cent. aqueous
8 Benzalkonium chloride (Zephiran (R) 0 1 per cent. tincture

9 Asterol tincture (R)
10 Sopronol solution (R)
11 Sodium thiosulfate solution 10 per cent.

*Stronger*

12 Tincture of iodine 1 to 7 5 per cent.
13 Salicylic acid tincture 2 to 10 per cent
14 Whitfield s tincture

Salicylic acid – 2 per cent.
Benzoic acid – 4 per cent.
in 70 per cent. alcohol

15 Resorcinol 2 to 25 per cent. in 70 per cent alcohol or tincture of benzoin
16 Castellani s paint
17 Ammoniated mercury 2 per cent. in calamine lotion

### C. PASTES

Soothing and protective

18 Lassar paste

Strong and keratolytic

19 Glaze and King paste

Salicylic acid 45 per cent.
Starch in petrolatum 5 per cent.

### D. OINTMENTS

The base is important. Petrolatum is greasy and non hydrophilic. Cholesterinized petrolatum (a substance used in many proprietary bases such as Aquaphor (R) and Qualatum (R)) is less greasy washable and somewhat hydrophilic. The Carbowax bases are non-greasy washable, and hydrophilic.

*Mild*

20 Boric acid ointment 2 to 10 per cent
21 Sulphur ointment 2 to 20 per cent.
22 Ammoniated mercury ointment 2 to 10 per cent

23. Sopronol (R) ointment
24. Desenex (R) ointment
25. Timofax (R) ointment
26. Asterol (R) ointment

*Intermediate*

27. Salicylic acid ointment 2 to 10 per cent.
    Sulphur and ammoniated mercury may be added for combined action
28. Whitfield's ointment
29. Salicylanalide ointment 2 per cent. in Carbowax base

*Strong*

30. Chrysarobin ointment 1 to 10 per cent.
31. Anthralin ointment 0.25 to 1 per cent.

*For secondary bacterial infection*

32. Neomycin ointment (R)
33. Bacitracin ointment (R)

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CHAPTER 88

# CULTURAL CHARACTERISTICS OF THE PATHOGENIC FUNGI AND OF SAPROPHYTIC FUNGI COMMONLY SEEN IN THE LABORATORY

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The diagnosis of a mycotic infection depends upon the demonstration of a fungus in tissues or exudates and upon its specific identification in culture. Not only do fungous diseases frequently mimic other pathological conditions such as bacterial infections and cancer but the individual mycoses exhibit a wide variability in their clinical picture. It is important therefore, to know the cultural characteristics of the pathogenic fungi. These include their gross and microscopic morphology as well as those physiological properties which influence the rate and character of their growth, pigmentation and spore production.

The large majority of the "true fungi" pathogenic for man (not including the Actinomycetes) have several features in common. With the exceptions of *Allescheria boydii* and *Piedraia hortai* they develop only asexual spores and therefore are classified among the Fungi Imperfecti and of these all except a small group associated with chromomycoses belong in the family Moniliaceae characterized by light-coloured or colourless mycelium. With few exceptions they have simple nutritional requirements and may be grown at room temperature on a sugar-peptone medium such as Sabouraud dextrose agar which is easily prepared from commercial products. In general the pathogenic fungi grow over a wide pH range and the use of either acid or alkaline media will allow their selective isolation from contaminating bacteria. Bacteria and some of the saprophytic fungi may also be suppressed by addition to the medium of antibiotics such as penicillin streptomycin and actidione. The general appearance of the pathogenic fungi on Sabouraud

dextrose agar with or without antibiotics has become a standard basis for the descriptions of these fungi. Additional media and different incubation temperatures are useful, however, for stimulating pigment production, sporulation, and special growth characteristics of certain species.

Media inoculated with clinical materials often are contaminated with non-pathogenic fungi originating either in the inoculum (sputum, pus, skin scrapings, etc.) or in the environment. Familiarity with the more common of these contaminants is important for several reasons: (1) So that they may quickly be recognized as being not pertinent to the case. (2) Because pathogens as a class cannot be differentiated by any simple rule from non-pathogens. (3) Because some of the so-called contaminants may, under appropriate conditions, manifest pathogenicity.

## PART I. CULTURAL CHARACTERISTICS OF THE PATHOGENIC FUNGI

The pathogenic fungi are described below as they appear on Sabouraud dextrose agar and on special media when such are of aid in their study. In those cases where identification cannot rest upon cultural characteristics alone, the proper physiological tests and animal inoculation procedures are indicated. In all cases, laboratory findings must be correlated with clinical observations before a diagnosis can be made.

## LIST OF THE PATHOGENIC FUNGI

A. Fungi which may cause cutaneous, subcutaneous, and/or systemic disease

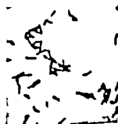
1. Actinomyces bovis
2. Allescheria boydii
3. Aspergillus fumigatus
4. Blastomyces brasiliensis
5. Blastomyces dermatitidis
6. Candida albicans
7. Coccidioides immitis
8. Cryptococcus neoformans
9. Histoplasma capsulatum
10. Hormodendrum compactum
11. Hormodendrum pedrosoi
12. Nocardia asteroides
13. Nocardia madurae
14. Phialophora verrucosa
15. Sporotrichum schenckii

Only those fungi are included which may regularly be obtained in culture. Some of the rare or doubtful dermatophyte species are omitted.

B Fungi which invade only skin, hair or nails

16. Epidermophyton floccosum
17. Microsporum audouini
18. Microsporum canis
19. Microsporum gypseum
20. Trichophyton concentricum
21. Trichophyton ferrugineum
22. Trichophyton megnini
23. Trichophyton mentagrophytes
24. Trichophyton rubrum
25. Trichophyton schoenleini
26. Trichophyton tonsurans
27. Trichophyton verrucosum
28. Trichophyton violaceum

1 *Actinomyces bovis Harz*, 1877 (Synonyms *A israeli Discomyces bovis Streptothrix actinomyces*) Cause of actinomycosis mycetoma.



Anaerobic on primary isolation, subcultures sometimes microaerophilic. Good growth anaerobically at 37° C on rich media such as veal or beef infusion-dextrose agar (pH 7 6—7 8). Some strains stimulated by the addition of blood to the medium. Surface colonies moist, white to cream-coloured, heaped, either smooth or verrucose and adherent, attaining a diameter of 1—3 mm after 7—10 days. (Most strains isolated from human lesions show a rough surface.) In deep agar shake tubes or anaerobic broth small white colonies with fuzzy or lobulated edges appear in the depths of the medium. Colonies consist of delicate (1 micron or less in width) branching mycelium, largely broken into fragments resembling diphtheroid and coccoid bacteria, Gram-positive and non-acid fast.

2. *Allescheria boydii Shear* 1921 (Synonyms *Monosporium apiospermum Scedosporium apiospermum Glenospora clapieri Indiella americana*) A cause of mycetoma and rarely of systemic infections.



Rapid-growing white fluffy colony becoming greyish-brown with white border reverse brownish-black. Mycelium hyaline, broad septate and branching Numerous unicellular elliptical conidia (7 4 $\mu$) borne singly or in clusters on tips of simple conidiophores. Conidiophores may be grouped in coremia Some strains produce dark-coloured spherical perithecia, 50—90 $\mu$ in diameter which when crushed liberate elliptical ascospores (5.5 × 3.5 $\mu$). Asci evanescent A number of strains isolated from human lesions form only asexual spores. These have been described as *Monosporium apiospermum* which represents the imperfect form of *Allescheria boydii*

3. *Aspergillus fumigatus* (Fresenius) Thom and Church, 1926. (Synonyms *A. avarus*, *A. bronchialis*) Cause of aspergillosis mycetoma.

Colony rapid-growing, flat, white at first, becoming greyish-green to very dark green. Surface velvety to floccose. Conidial heads columnar. Conidiophores smooth-walled. Vesicles flask shaped typically fertile over upper half. Sterigmata in one series, crowded. Conidia globose, echinulate, green. No perithecia.

4. *Blastomyces brasiliensis* (Splendore) Conant and Howell 1941 (Synonyms *Paracoccidioides brasiliensis*, *P. cerebriformis*, *P. tenuis*, *Zymonema brasiliense*, *Lutziomyces histosporocellularis*) Cause of South American blastomycosis.

*Mycelial phase.* Colonies on Sabouraud dextrose agar at 25° C very slow growing, heaped, usually irregularly dented, and covered with short, white to brownish, downy aerial mycelium. Wrinkled or cerebriform glabrous strains occur. Microscopically poorly developed mycelium with a few oval to round, single-celled conidia on short stalks.

*Yeast phase.* On blood agar at 37° C growth is yeast like, cream to tan, with smooth or rough surface consisting microscopically of large (10—60 $\mu$), single or multiple budding, yeast-like cells. Buds on a single cell may be numerous and each about 1—2 $\mu$ in diameter, or fewer and much larger, varying considerably in size and shape. Mycelial phase may be converted to yeast phase by either animal inoculation or culture on blood agar or other media at 37° C.

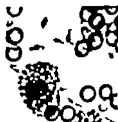
5. *Blastomyces dermatitidis* Gilchrist and Stokes, 1898. (Synonyms *Oidium dermatitidis*, *Cryptococcus gilchristi*, *Glenospora gammeli*, *G. brevis*, *Zymonema gilchristi*, *Z. dermatitidis*) Cause of North American blastomycosis.



*Mycelial phase.* Colonies on Sabouraud dextrose agar at 25° C at first flat, moist and glabrous soon covered with a white cottony growth becoming brownish with age. Microscopically oval to pyriform conidia (3—4 $\mu$ in diameter) occur singly on the hyphae or on short conidiophores. Thick-walled chlamydospores in old cultures.

*Yeast phase* On various media at 37° C a whitish-yellow yeast-like growth with smooth or rough surface, composed of thick-walled budding cells 7—25 $\mu$ in diameter Usually each cell produces only one bud which is separated from the mother cell by a broad base. Mycelial phase may be converted to yeast phase by either animal inoculation or culture on blood agar or other media at 37 C.

6. *Candida albicans* (Robin) Berkhout, 1923 (Synonyms *Oidium albicans Endomyces albicans Syringospora albicans Monilia albicans M psilosis*) Cause of moniliasis (candidiasis) (thrush).



*Sabouraud dextrose agar* Colony cream-coloured, smooth, pasty with a yeast like odour Composed of small (2—4 $\mu$) oval, budding, thin-walled, yeast like cells. Old cultures may show pseudomycelium.

*Cornmeal agar* Thin plates of this medium are inoculated by cutting through the agar A fringe of pseudomycelium and true mycelium extends into the agar Growth composed of branched hyphae bearing clusters of blastospores at the septa and terminal thick walled chlamydospores.

The appearance of numerous thick walled chlamydospores on corn meal agar is diagnostic of this species. If chlamydospores do not appear sugar fermentation tests may be made Results for this species dextrose—acid and gas maltose—acid and gas sucrose—acid (slight) lactose—no acid or gas. *C albicans* is lethal for rabbits when injected intravenously

7 *Coccidioides immitis* Rixford and Gilchrist 1896. (Synonyms *Psorodesma cutiferiformis Blastomycoides immitis Geotrichum immite Glenospora metaeuropea G loutsanensis*)



Small, moist, membranous colonies after 3—4 days. Later spiny outgrowths appear and culture is gradually covered with white, woolly aerial mycelium that becomes brownish with age Aerial growth frequently moist and matted in central area, remaining fluffy at periphery Mycelium fine, septate branching Mature sporulating hyphae forming arthrospores from alternate cells. Arthrospores typically thick walled, square or rectangular and readily separated, each retaining fragments of the intervening empty cells

Cultures are sometimes difficult to differentiate from the saprophyte, *Oospora sp.* Animal inoculation is advised to obtain the characteristic tissue form spherules 20—200 $\mu$ in diameter the largest of which are thick walled and filled with numerous small endospores.

Note In handling cultures of *C immitis* due precaution must be taken to prevent dissemination of the highly infectious arthrospores. Never make petri dish cultures, always use test tubes, and flood the slant with sterile saline containing a wetting agent before withdrawing any portion of the colony

8. *Cryptococcus neoformans* (Sanfelice) Vuillemin, 1901 (Synonyms: *C. hominis*, *C. histolyticus*, *C. meningitidis*, *Torula neoformans*, *T. histolytica*, *Debaryomyces hominis*) Cause of cryptococcosis (torulosis, yeast meningitis).



Colony white to tan, pasty with smooth surface or mucoid (occasionally very mucoid) and semi-fluid. Composed entirely of spherical budding cells averaging 5 μ in diameter. Most cells surrounded by large capsule (easily visible in India ink preparations), which may be narrow in non-mucoid isolates. Mycelium not formed on corn meal agar or any other medium.

To distinguish from saprophytic cryptococci, it is necessary to determine that the isolate will grow at both 25° C and 37° C, and that it is virulent for mice.

9. *Histoplasma capsulatum* Darling, 1906 (Synonyms: *H. pyriforme*, *Cryptococcus capsulatus*, *Torulopsis capsulatus*, *Posadasia capsulata*, *P. pyriforme*) Cause of histoplasmosis.



*Mycelial phase.* Colonies on Sabouraud dextrose agar at 25° C white and cottony with surface at times yellowish-brown. Mycelium hyaline, septate, broad (2.7 μ in diameter), bearing large, spherical, tuberculate, thick walled spores (7—18 μ in diameter). Smaller smooth-walled spores (2.5—4 μ) also formed. Both types borne on short, simple conidiophores or directly from the mycelium.

*Yeast phase.* Growth on blood agar at 37° C moist, creamy-white to tan, yeast like, but with smooth or rough surface and may show a mycelial fringe. Composed of small round or oval cells 1—5 μ in diameter. Oval cells often pointed at one pole. Mycelial phase may be converted to yeast phase by either animal inoculation or culture on blood agar at 37° C.

To differentiate the culture from the saprophyte *Sepedonium sp.* which it resembles microscopically and which may also produce a yeast-like growth under certain conditions, intraperitoneal injections of spores or mycelial elements into mice should be undertaken to obtain the development of intracellular yeast-like cells in the animal.

10. *Hormodendrum compactum* Carrion, 1935. (Synonyms: *Fonsecaea compactum*, *Phialoconidiophora compactum*, *Phialophora compactum*) Cause of chromoblastomycosis.

Colonies very slow growing (3 cm or less in 6 weeks), heaped, dark brown to black or greenish-black with velvety surface, often with tufts of coarse dark aerial hyphae; reverse black. Mycelium brown, coarse, closely septate. Three types of sporulation may be found



a. *Hormodendrum type* (predominant). Conidia unicellular, spherical to barrel shaped in short, branching chains. Individual conidia pressed closely together in chain with broad septa between them.

b. *Acrotheca type*. Conidia similar to above but attached singly on tip and along sides short, straight or irregularly swollen conidiophores.

c. *Phialophora type* (rare). Similar to that of *P. verrucosa* *i.e.*, conidiophores flask shaped with terminal cup-like structure. Tiny conidia extruded singly and successively from cup where they remain in clusters until disturbed.

11. *Hormodendrum pedrosoi* Brumpt, 1922. (Synonyms: *Phialophora pedrosoi*, *Acrotheca pedrosoi*, *Hormodendrum algeriensis*, *Fonsecaea pedrosoi*.) Cause of chromoblastomycosis.



Colonies slow-growing, dark brown to black or greenish-black, slightly heaped at the centre with a greyish velvety surface growth, reverse black. Mycelium brown, septate. Three types of sporulation may be found:

a. *Hormodendrum type* (predominant). Conidia single-celled, oval, olive-green to brown, connected in branching chains by thick disjunctors.

b. *Acrotheca type*. Conidia similar to above but often elongate, borne on tip and along sides of simple, sometimes knobby conidiophores.

c. *Phialophora type*. Similar to that of *P. verrucosa*, *i.e.*, conidiophores flask shaped with terminal cup-like structures. Tiny conidia extruded singly and successively from cup where they remain in clusters until disturbed.

12. *Nocardia asteroides* (Eppinger) Blanchard, 1896. (Synonyms: *Cladothrix asteroides*, *Streptothrix asteroides*, *Actinomyces asteroides*, *A. gypsoides*). Cause of nocardiosis, mycetoma.



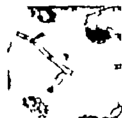
Aerobic, growing well on Sabouraud dextrose agar and other media at 25° C or 37° C. Colony heaped, granular or membranous, yellow to orange-coloured, but often white to pinkish on primary isolation and may remain so. Pigment production often better on Czapek's agar. Grows as a soft pellicle on litmus milk, turning it alkaline with no coagulation. Colony composed of fine, branching, non-sporulating mycelium (1 $\mu$ or less in diameter), fragmenting readily into bacillary and coccoid forms. Gram-positive and partially acid fast (using Kinyoun's or Ziehl-Neelsen stain followed by 15 seconds decolorization with 3 per cent. HCl in ethyl alcohol). Acid fastness often enhanced by growth on litmus milk.

To differentiate from saprophytic strains, animal inoculations should be made. Pathogenic strains cause death of guinea pigs when inoculated intraperitoneally especially when suspended 1 1 in 5 per cent. gastric mucin.

13 *Nocardia madurae* (Vincent) Blanchard, 1896. (Synonyms *Streptothrix madurae Oospora madurae Actinomyces madurae Discomyces madurae Nocardia indica*.) Cause of mycetoma.

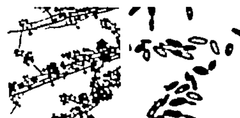
Aerobic, growing on Sabouraud dextrose agar at 25° C and 37° C. Very slow growing, heaped, glabrous waxy wrinkled colonies at first cream coloured, later becoming pink to red Peptonizes milk. Composed of long, fine, branching, non-sporulating mycelium (1 μ or less in width). Gram-positive, but not acid fast. Not pathogenic for laboratory animals.

14 *Phialophora verrucosa* Thaxter 1915. (Synonyms *P macrospora Cadophora americana*.) Cause of chromoblastomycosis.



Colony slow-growing, brown to black or greenish-black with greyish velvety surface growth reverse black. Mycelium brown, septate. Conidiophores flask shaped, terminal or lateral, consisting of three parts base, neck, and cup. (5—12 × 2—4 μ). Single-celled, oval, hyaline conidia (2—4 × 1—2 μ) are extruded singly and successively and tend to remain in cluster at lip of cup until disturbed.

15 *Sporotrichum schenckii* Matruchot 1910. (Synonyms: *S beurmanni S asteroides S equi S jeanselmei S councilmani Sporothrix schenckii*) Cause of sporotrichosis.



*Mycelial phase* Colonies on Sabouraud dextrose agar at 25 C at first small, white moist, and yeast-like. Later becoming wrinkled and membranous, developing areas of brown and black pigment. Entire colony may be come brownish-black. Some strains develop a short aerial mycellum which may be aggregated into spines. Microscopically fine, branching, septate mycelia bearing oval to round conidia singly on delicate sterigmata and in flower-like clusters on simple conidiophores.

*Yeast phase* On cystine-blood agar at 37° C, growth is cream coloured, moist, and yeast-like composed of tiny (3—5 μ) oval or cigar-shaped budding cells. Mycelial phase may be converted to yeast phase by either animal inoculation or culture on cystine-blood agar at 37 C.

16 *Epidermophyton floccosum* (Harz) Langeron and Milochevitch, 1930 (Synonyms *E inguinale E cruris E plicarum E. clypeiforme Trichophyton intertriginis T inguinale T cruris*) Cause of tinea corporis, tinea pedis tinea ungulum.



Colony slow-growing light olive green or yellow green to tan, usually flat with a finely powdery surface. Old colonies may show central knob and radial grooves. Tufts of white, fluffy sterile (pleomorphic) growth develop rapidly on surface of colony Macroconidia often numerous 2—4 celled large broad, blunt to clavate, with smooth, thin walls borne singly or more characteristically in groups of 2 or 3 Chlamydospores usually numerous. Spirals rare, microconidia absent

17 *Microsporum audouini* Gruby 1843. (Synonyms *M villosum M umbonatum M velveticum M tardum M tomentosum M depauperatum Sabouraudites audouini Trichophyton decalvans*) Cause of tinea capitis tinea corporis.



Colony slow-growing flat, velvety with whitish-tan to brownish surface Reverse light salmon, orange-tan, or non pigmented. Growth on rice grains very poor. Mycelium usually sterile with many chlamydospores. Microconidia rare clavate usually sessile on the hyphae Macroconidia extremely rare in some strains, large, irregularly spindle-shaped, thick walled with smooth or rough surface Abortive and highly irregularly shaped macroconidia are most commonly seen their production may be stimulated by growth on media enriched with yeast-extract.

18 *Microsporum canis* Bodin 1902. (Synonyms *M felineum M equinum M lanosum M caninum Sabouraudites lanosus S felineus S lanosus*) Cause of tinea capitis tinea corporis



Growth rapid Surface at first white, silky with bright yellow pigment in peripheral growth Reverse yellow orange. After 2—4 weeks, surface dense, tan, cottony sometimes in irregular tufts or concentric rings, often with central knob of heavier growth. Reverse becomes dull orange brown Grows well on rice grains. Macroconidia numerous, 8—15 celled, spindle-shaped, often terminating in a distinct knob and with thick verrucose walls. Microconidia few clavate, usually sessile on the hyphae.

19 *Microsporum gypseum* (Bodin) Guiart and Grigorakis 1928. (Synonyms: *M fulvum M flavescens M scorteum M xanthodes Achorion gypseum Sabouraudites gypseus*) Cause of tinea capitis, tinea corporis.



Growth rapid, colony flat with irregularly fringed border and coarsely powdery surface ranging from light ochre to deep cinnamon brown Tufts of white, fluffy sterile (pleomorphic) growth develop rapidly on surface of colony Good growth on rice grains. Macroconidia numerous, 3—9 celled, ellipsoid, shorter and broader than those of *M canis* and with thinner, rough walls. Microconidia rare clavate, usually sessile on the hyphae.

20. *Trichophyton concentricum* Blanchard, 1896. (Synonyms *T mansoni T castellani Endodermophyton concentricum E castellani E. indicum E tropicale E. roquettei*) Cause of tinea imbricata (tokelau).



Colony slow-growing, heaped, deeply folded, at first glabrous and white, becoming tan to brownish. Some white down may develop irregularly on surface reverse becomes yellow to golden. Composed of irregular mycelium and numerous chlamydospores. A few microconidia in downy surface growth, small, clavate, sessile on hyphae

21 *Trichophyton ferrugineum* (Ota) Langeron and Milochevitch, 1930. (Synonyms *Microsporum ferrugineum M aureum M orientale M japonicum*) Cause of tinea capitis, tinea corporis.

Colonies slow-growing, flat with regular radial grooves or heaped and cerebriform Surface glabrous and wax-like or covered with a short aerial mycelium. Usually shades of yellow to red-brown (rust-coloured) some strains show no pigment ( riety album). Microscopically thin, twisted, irregular mycelium with abundant chlamydospores

22. *Trichophyton megnini* Blanchard, 1896. (Synonyms *T rosaceum T rosaceum T roseum Ectotrichophyton megnini Megatrichophyton megnini M roseum Sabouraudites megnini*) Cause of tinea capitis, tinea barbae tinea corporis



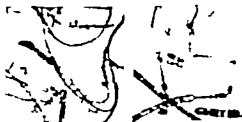
Colonies slow-growing, flat, usually with regular radial grooves. Surface velvety at first white then pink and later deep rose Edge of colony smooth or scalloped. Reverse rose to deep red. Pigment non-diffusible. No growth on inorganic nitrogen-dextrose medium. Requires L-histidine for growth. Microconidia often numerous, small, pyriform, along sides of mycelium or in terminal clusters Macroconidia rare, —8 cells, pencil-shaped to very slightly clavate.

23 *Trichophyton mentagrophytes* (Robin) Blanchard, 1896. (Synonyms *T granulosum* *T radiolatum* *T lacticolor* *T niveum* *T radians* *T denticulatum* *T persicolor* *T farinulentum* *T asteroides* *T interdigitale* *T kaufmann-wolf* *T pedis* *T "C" Hodges*) Cause of tinea pedis tinea capitis tinea unguium, tinea barbae tinea corporis



Colony rapid-growing, flat, disc-like, white to cream, occasionally yellow or pink. Border regular or fringed. Texture from coarsely granular to powdery to downy or cottony Reverse usually rose-brown, occasionally yellowish, orange or deep red. Microconidia very numerous, small globose, borne singly along mycelium or in pine-tree like terminal clusters. Macroconidia rare or abundant depending on strain, 2—5 celled, thin-walled, slightly club-shaped. Production of macroconidia stimulated by growth on wort agar Tightly wound spirals, nodular bodies may be numerous. In downy to fluffy strains microconidia may be thin and delicate and occur only along sides of hyphae, and macroconidia may be rare. No red pigment produced on corn meal-dextrose agar

24 *Trichophyton rubrum* (Castellani) Sabouraud, 1911 (Synonyms *T purpureum* *T rubidum* *Epidermophyton perneti* *E salmoneum* *T "A" Hodges* *T "B" Hodges*) Cause of tinea pedis tinea unguium, tinea corporis, tinea capitis tinea barbae.



Colony slow-growing flat or heaped, with a white, fluffy surface Reverse at first colourless, becoming deep wine red. Occasional strains with a powdery to coarsely granular surface white to cream, becoming rose to deep red. These strains also deep red on reverse Microconidia rare in fluffy strains, thin and delicate and occurring only along sides of hyphae Microconidia common in granular strains, more globose and occurring along the mycelium and in terminal pine-tree-like clusters. Macroconidia rare in most strains but most common in granular cultures, usually elongate and thin with blunt ends, 3—8 cells Production of macroconidia stimulated by growth on heart infusion-tryptose agar Red pigment produced on corn meal-dextrose agar

25. *Trichophyton schoenleini* (Lebert) Langeron and Milochevitch, 1930 (Synonyms *Oidium schoenleini Achorion schoenleini*) Cause of favus (tinea corporis tinea capitis tinea unguium).



Colony slow-growing, usually irregularly heaped and folded, tough and leathery tending to crack the agar Surface white to tan, glabrous or downy Occasional strains grow largely submerged in the agar Growth *not* stimulated by addition of vitamins to the medium. Mycelium highly irregular Coarser hyphae tend to become knobby and clubbed at ends (chandeliers). Chlamydospores usually numerous. Microconidia very rare.

26. *Trichophyton tonsurans* Malsten, 1845. (Synonyms *T crateriforme T effractum T fumatum T umbilicatum T regulare T exsiccatum T polygonum T epilans T flavum T cerebriforme T plicatile T sulfureum T sabouraudi T acuminatum*) Cause of tinea capitis tinea corporis tinea barbae tinea pedis tinea unguium.



Growth fairly rapid colonies extremely variable, usually irregularly folded with acuminate or crateriform centres. Surface downy to velvety cream to yellow to tan or rose Border regular or scalloped. Reverse reddish-brown, yellow to tan, or purplish. Microconidia numerous, usually small and clavate in young cultures, becoming larger and highly irregular in size and shape in old cultures, borne along sides of hyphae or in loose terminal clusters. Macroconidia rare, 2—4 celled, with thin smooth walls, usually slightly clavate but many irregular and abortive. Production of macroconidia stimulated by growth on wort agar or in wort broth hanging drop cultures. Mycelium becomes thick and irregular in old cultures and chlamydospores are very numerous.

27 *Trichophyton verrucosum* Bodin, 1902. (Synonyms: *T faviforme T album T ochraceum T discoides*) Cause of tinea capitis tinea barbae tinea corporis.

Growth extremely slow-growing, of four general types wax like or white, heaped and folded (variety album) disc-shaped and downy (variety discoides) glabrous verrucose, and ochraceous (variety ochraceum) glabrous, verrucose and gray (variety verrucosum) Colonies at first glabrous, sometimes developing white

powdery or downy surface growth. No growth on vitamin-free media. Growth of most strains stimulated by thiamin or thiamin and inositol. Microscopically on Sabouraud dextrose agar usually only sterile irregular mycelium with numerous chlamydospores, often in chains. Clubs and chandeliers occasionally seen. On thiamin-enriched media, mycelium more regular and microconidia may be numerous. They are small, clavate, borne singly along the hyphae or in terminal clusters. Macroconidia rare, 3—5 celled, thin-walled, slightly clavate, varying considerably in size and shape.



28 *Trichophyton violaceum* (Sabouraud) Bodin 1902. (Synonyms *T. glabrum*, *Achorion violaceum*, *Bodinia violacea*, *Sabouraudites violaceus*.) Cause of tinea capitis, tinea corporis, tinea unguium.

Colony slow-growing, heaped, verrucose, moist and glabrous. Cream-coloured at first, becoming deep violet to purple. With age pigment is lost and colony becomes covered with greyish-white aerial mycelium. Microscopically usually only irregular mycelium and chlamydospores. Microconidia rare on Sabouraud dextrose agar, often numerous on thiamin-enriched media, thin and elongate, borne both laterally and in clusters. Macroconidia absent on ordinary media, occasionally seen on thiamin-enriched media, 2—5 cells, irregularly clavate.



## PART II SAPROPHYTIC FUNGI COMMONLY SEEN AS CONTAMINANTS

A selection of the most common and cosmopolitan of the contaminating fungi is presented, since it is impossible to describe here all of the tremendous number of saprophytic fungi which might be encountered in widely varying localities. Because colonial appearance varies considerably and since classification is based primarily upon microscopic structures, the photographic illustrations will be confined to the latter, with typical colony characteristics indicated in the legends. These are described as they appear on Sabouraud dextrose agar. Genera only will be represented, since identification of species is, in general, a specialized study which is unnecessary for the present purpose.

1 *Alternaria sp*



Colony rapidly-growing, dense, grayish or green-gray becoming black. Surface often overgrown with looser white to gray aerial mycelium. R verse black. Mycelium microscopically dematiaceous, septate. Conidiophores simple, with simple or branched chains of large, oliv aceous, obovate or obclavate conidia, septate both transversely and longitudinally. Apex of conidium usually attenuate. *Stemphylium* is similar but conidia non-attenuate and not in chains.

2. *Aspergillus sp*



Colony colour various, most commonly blue-green or yellow-green when sporulating, sometimes black (*A niger*), white, tan, etc. Surface velvety floccose, or fasciculate, usually with abundant sporulation. Mycelium hyaline conidiophore consisting of elongate stalk with inflated tip (vesicle), from which arise one or more series of sterigmata, ultimately bearing unbranched chains of conidia. Conidia one-celled spherical to elliptical, smooth or rough, hyaline or pigmented. Some species producing also perithecia and asci with characteristic ascospores. Occasionally pathogenic, especially *A. fumigatus*

3. *Cephalosporium sp*



Fairly rapid growth, often flat and moist at first, becoming loose-cottony White, rose-coloured, or gray My celium hyaline, bearing slender unbranched, usually attenuate conidiophores, commonly alternating in rows on opposite sides of hypha. Conidia elliptical to elongate, usually one-celled but sometimes 1—2 septate, borne apically in globose clusters often encased in a mucoid mass.

The conidial clusters are readily disrupted and the conidia scattered upon handling, so that microscopic examination through he side of the culture tube or by means of slide cultures is usually required

4 *Chaetomium sp.*

Colonial appearance various, usually of dense turf grayish-white to olive-gray or black, with macroscopically visible perithecia (1—7 mm diam ) scattered or gre garious, free on superficial mycelium. Hyphae septate, hyaline or olivaceous. Perithecia globose to ellipsoid, thin-membranous, olivaceous to dark brown, cred wholly or in part with numerous long, olivaceous to brown setae and con ning evanescent cla ate asci. Ascospores eight in each ascus simple, hyaline to dark brown, globose to lemon-shaped, often apiculate at both ends.

5 *Cryptococcus sp*

Colony yeast like white to cream-coloured, composed of oval to round, budding yeast cells. No mycelium Ascospores never produced.




6 *Curvularia sp.*

Rapid growth, velvety or low-cottony brown black Conidia oval-elongate 4—5-celled, brown or olivaceous, the third cell larger than the others and with unequal sides causing conidium to appear curved or geniculate clustered at and near tips of gnarled dematiaceous conidiophores similar to those of *Helminthosporium*

7 *Fusarium sp*



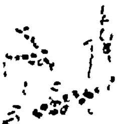
Colony rapidly growing cottony or woolly usually with much aerial mycelium Often white but usually with some pigment in either aerial or surface growth violet yellow ochre, salmon rosy etc. Macroconidia sickle-shaped, pointed at both ends, several-celled, colourless o pale-coloured, clustered or whorled on branches of short conidiophores Microconidia, when present similar to those of *Cephalosporium*



8. *Fusidium sp*

White, fine cottony colony growing fairly rapidly Mycelium hyaline septate, with long, unbranched chains of conidia arising from undifferentiated hyphal branches. Conidia spindle-shaped, pointed at both ends, hyaline to pale green.

9 *Geotrichum sp*



White mealy yeast like growth with submerged peripheral hyphal strands. Sometimes with very short aerial mycelium Sporulating heavily by fragmentation of hyaline septate hyphae into large, rectangular arthrospores commonly germinating at one corner

10. *Graphium sp*

Growth slow t moderately rapid, at first glabrous and moist or dry white to brownish, later developing velvety or sparse woolly aerial mycelium. Coremia visible to the naked eye as short (1—2 mm), thick, black stalks surmounted by



white spore masses. Reverse light brown, speckled with black where the coremia occur. Microscopically the coremia consist of closely packed bundles of parallel hyphae, dark brown on the periphery and lighter in the interior flaring at the apex and producing singly at the hyphal apices numerous small, hyaline, pyriform to elongate conidia, sometimes embedded in mucus.

Conidia occur also in small clusters on individual hyphae, either sessile or on simple conidiophores, resembling *Sporotrichum sp*

11 *Helminthosporium sp.*



Rapidly-growing grayish-brown colony with velvety to woolly aerial mycelium, often matted in the central area but usually fluffy at the edges. Hyphae thick and dark, bearing short, unbranched conidiophores with elongate, multiseptate, thickwalled, brown conidia. Conidiophore initially producing a singly conidium at the apex, then elongating beyond this point and producing additional conidia in similar manner thus assuming the appearance of a tortuous club.

12. *Hormodendrum sp.*



Colony olive-green to brown, gray or black thin-membranous, powdery or velvety becoming heaped and folded. Sometimes with tufts of gray woolly aerial mycelium. Hyphae septate, brown or olivaceous, with simple conidiophores bearing branched chains of spores. Conidia one or two-celled, globose to elliptical, brown or ol aceous, separated in the chain by dark disjunctors.

13. *Humicospora sp.*



Growth fairly rapid, aerial portion consisting of compact light gray mycelium with dark gray centre often with light ol vaceous tinge. Reverse pale brown, with concentric darker rings and black centre. Conidia numerous, brown, unicellular round to pyriform, thick walled, sessile on sides of hyphae or borne on very short stalks.

14 *Mucor sp.*

Voluminous growth, completely filling tube within a few days, composed of long

fibered, coarse woolly mycelium, white becoming gray sprinkled with numerous black dots (sporangia). Mycelium microscopically hyaline, coarse, non-septate. Fruiting body consisting of long stalk (*sporangiophore*) surmounted by spherical *sporangium*. Sporangium dark walled, filled when mature with spherical spores and a basal *columella*, a projection of the stalk. Sporangium rupturing when mature and releasing *spores*, leaving the columella, which is often collapsed. Sporangiophores *branched*, arising singly, irregularly on the mycelium, bearing sporangia at all apices. Heavy walled dark zygospores (sexual spores) occasionally present.





15. *Nigrospora sp.*

Rapidly-growing white, cottony colony, becoming gray with considerable aerial mycelium. Reverse black. Conidia large, subspherical, *jet-black*, smooth, singly on inflated apices of branched hyaline conidiophores. Mycelium hyaline turning dark.



16. *Oospora sp.*

Rapidly growing, dense, white cottony aerial mycelium, turning cream or tan upon sporulation. Hyphae fragmenting at septa to form hyaline, rectangular arthrospores.



17. *Paecilomyces sp.*

Brownish to fuscous, thin, spreading, powdery to velvety colony, sporulating abundantly. Hyaline hyphae bearing *Penicillium*-like heads and also single sterigmata with chains of elliptical conidia. Sterigmata flask-shaped, tapering distally.



18. *Penicillium sp.*

Colonies rapidly-growing, commonly in shades of green ... blue-green, but colour various. Surface usually powdery o... el...ety as a result of abundant sporulation on aerial mycelium. Spore-bearing hyphae microscopically forming a "penicillus" or brush-like structure by repeated branching. Conidia one-celled, globose to elliptical, smooth ... rough, sometimes pigmented, occurring in unbranched chains arising from ultimate branches (sterigmata) of the conidiophore.



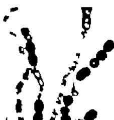


The numer... species are identified on the basis of manner of branching of the conidiophore, shape and colour of the conidia, and characteristics of the perithecium and asci, when present.



19 *Pullularia sp*

Young colonies at first white or pinkish, yeast-like, spreading soon developing darker areas and at length turning entirely lustrous-black or green-black. Growth pasty and smooth centrally with wide fringe of fern-like submerged mycelium. Old cultures sometimes developing limited aerial mycelium. Young hyphae delicate, thin-walled, hyaline, producing numerous elliptical conidia by budding. Conidia budding secondarily to form clusters, attached to hyphae or free in liquid mounting media. Older hyphae dark, coarse thick walled, closely septate, forming chains of brown, cuboid cells, eventually also producing hyaline elliptical conidia by budding from short germ tubes.



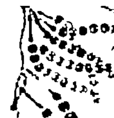
20 *Rhizopus sp.*



Similar to *Mucor* but *sporangiophores unbranched*, clustered at nodes opposite *rhizoids* (root-like hyphae) along a horizontal runner (*stolon*).

21 *Rhodotorula sp.*

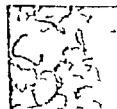
Colony yeast-like or bacteria-like, pasty to mucoid orange, pink or red (called "pink yeast") Growth consisting entirely of oval, budding yeast cells, rather small, usually budding singly similar to *Cryptococcus sp*



22 *Scopulariopsis sp*

Thin, light brownish, heavily-sporulating, powdery colonies, growing at a moderate rate. Mycelium hyaline. Long, unbranched chains of conidia arising from short, simple truncate conidiophores as well as from *Penicillium*-like branched forms. Conidia large (6—7 $\mu$), lemon-shaped, truncate at base double walled echinulate (sometimes obscurely).

23 *Streptomyces sp*



Colonies small, dry leathery usually adherent to substrate Colour various, commonly white or whitish and chalky Often with strong musty odour and discoloration of agar Mycelium extremely slender (1 $\mu$), branched, bearing straight or variously curved chains of tiny conidia on terminal aerial branches. Distinguishable by presence of aerial conidia and absence of extensive fragmentation from *Nocardia*.

24 *Syncephalastrum sp.*



Similar to *Mucor* in colonial appearance and mycelial characteristics. Sporangiophores branched each apex greatly swollen and bearing numerous radiating *tubular sporangia* each sporangium containing a single chain of two to several single celled spores.

25 *Trichoderma sp*



Colony developing rapidly floccose or woolly initially white but commonly becoming bright green upon sporulation. Mycelium hyaline, bearing branched, erect conidiophores. Ultimate branchlets flask-shaped, generally opposite or whorled, each bearing apically small spherical, bright green conidia in a globose cluster

26 *Verticillium sp*



Rapidly growing, usually forming a loose turf often becoming powdery upon sporulation, commonly white but some species green, yellow or red. Mycelium hyaline, bearing erect, septate, verticillately branched conidiophores, the terminal branches usually flask shaped and attenuate Conidia round to elliptical, single celled, hyaline or light-coloured, borne singly or in small clusters and easily dissociated from the conidiophore

# DISEASES DUE TO ALLERGY MALNUTRITION AND METABOLIC DISTURBANCES

# PROBLEMS OF ALLERGY

J. TAS

Jerusalem

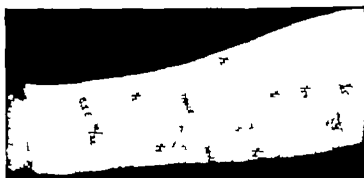
## DEFINITION

Allergy plays an important role in tropical dermatology Apart from its role in infections and infestations we encounter it in insect bites and dermatitis from plants. Occupational dermatoses, which are often allergic, are relatively unimportant in the tropics but with further industrialization they will probably get the same preponderance they have in technically more developed countries. It should not be forgotten that sweating is a predisposing factor as is intensive irradiation.

JADASSOHN was one of the first to study problems of dermatological allergy and introduced the *patch-test* (1896). The term allergy was coined by VON PIRQUET (1906) and defined by him as an "altered capacity to react" as *e.g.* the reaction of a vaccinated person to the small pox virus, of a syphilitic to the syphilis-virus, of a tuberculous patient to tuberculin, of a serum-treated patient to serum. All these reactions are different in persons who have never been in contact with these substances. Their reactivity is altered For this general concept of altered capacity to react I propose the term allergy"

Allos" means deviation from the original state, the reaction of the normal person as in allorhythmia, allotropia. By this definition is meant not only an acquired hypersensitivity but also a lessened sensitivity However in the course of time it has become usual to speak of allergy as an *acquired hypersensitivity* and it is in that sense we

shall use it here. The allergic reaction is supposed to be a result of the clash of the allergens (antigenic substances) with an antibody which has been formed by the afflicted individual in a previous contact with the allergen. In this clash histamine like and or acetylcholine like substances are supposed to be liberated, giving rise to the reactions (LEWIS) It is not possible in all cases to prove the presence of antibodies, but if their presence is probable we speak nevertheless of allergic reactions Now distinction should be made between *contact dermatitis* which always implies an allergic aetiology and *toxic dermatitis* which occurs at the first contact with the causative agent called *primary irritant* Apart from clinical and serological methods we have



928 Rare case of provocation of initially negative tuberculin reactions (applied 14 to 30 days previously) by the repeated application of 50 per cent human tuberculin test The reaction could not be regarded merely late, since it became positive simultaneously with that carried out later
Figures indicate concentrations.
*(S [illegible] – Amsterdam)*

two ways of demonstrating allergy towards specific allergens

(1) Epicutaneous patch tests (eczematous reactions)

(2) Cutaneous tests which can be performed by

- (a) intracutaneous injections
- (b) superficial scratching
- (c) superficial pinpricking
- (d) iontophoresis

The reactions to cutaneous tests may be either of the *immediate*

*wheal-type* (urticarial) or of the delayed *tuberculin-type* (papular). The former, which reach their maximum intensity in 10–20 minutes, are probably caused by antibodies which also circulate in the blood and are as a rule associated with the γ-globulin fraction of the serum proteins. These antibodies may be demonstrated by transfer of serum from a patient to a healthy volunteer and the subsequent injection of the allergen. If an urticarial reaction develops at the site of injection, the test is called positive (PRAUSNITZ-KUESTNER technique). The delayed papular reactions which reach their maximum in 24–48 hours (or after weeks, *e.g.* MITSUDA test in leprosy) are probably caused by cell-bound antibodies. The lymphocytes (and perhaps other cells as well) are the carriers of these antibodies. This has been proved experimentally—for tuberculin sensitivity—by CHASE and in man by LAWRENCE. The latter succeeded in transferring passively tuberculin sensitivity through leukocytes of the circulating blood.

## I. PATCH-TEST (ECZEMATOUS REACTION)

It is relatively easy to sensitize animals and humans experimentally to certain complicated and simple substances. BLOCH succeeded invariably in sensitizing guinea pigs to primula extract. Even in this seemingly simple instance of sensitization many factors known and unknown play a role. The experience of SULZBERGER is interesting. He had worked in Europe on cutaneous sensitization of guinea pigs by neoarsphenamine and *para*phenylenediamine:

When I arrived in New York City and visited KARL LANDSTEINER at the ROCKEFELLER Institute, I found that this most eminent immunologist of our time had tried to repeat our European work with simple chemicals (arsphenamine, *para*phenylenediamine and phenylhydrazine) and had failed to sensitize a single guinea pig. LANDSTEINER and all his co-workers were most polite but (mark this well!!) were all highly sceptical as to the possibility of experimentally sensitizing the skin of any laboratory animal or man with a simple chemical. I then proceeded to roll up my sleeves and to show them". I used the same techniques, dosage etc., I had employed at Breslau and Zurich, the same age and weight, size and colour of guinea pigs. Despite repeated attempts and numerous series of experiments not one of the ROCKEFELLER Institute animals could be sensitized. I need not tell you that my face was red". Then began a great carrying to and fro of guinea pigs, young and old, pregnant and newborn, of neoarsphenamine, of glass ware, of syringes, of needles, of water and of fodder between the Universities of Breslau and of Zurich and the ROCKEFELLER Institute in New York City. Finally, after

about four years, LANDSTEINER, FREI, PHILIP LEVINE, MERRILL CHASE, R. L. MAYER and I all agreed that it was an indisputable fact that even American guinea pigs could be skin-sensitized with a simple chemical like neoarsphenamine. Moreover we were all equally convinced that the susceptibility to skin sensitization on the part of guinea pigs varied in a tremendous range. In some of the series in New York there were zero-sensitizations, while the incidence rose to 50 % or more in other series—still far below the high rates of 80 % to 90 % achievable during the winter in Breslau! We began to try to elucidate the reasons for these variations. MERRILL CHASE then showed selective breeding from easily sensitized guinea pigs can produce families of animals highly susceptible to such sensitization and vice versa. Thus, hereditary factors in the guinea pigs are important—but surely not the whole story

Something in certain kinds of green fodder the vitamin-C content of the diet, the season in which the experiment takes place even the manufacturer's batch of the drug, are also of influence. As MAYER, OHR and SIMON and I have shown, each of these factors can be influential in raising and lowering the susceptibility to sensitization, but neither alone nor in combination do they account for all the variations observed. In other words, we have gathered much knowledge but are yet far from knowing all or even the most decisive factors bringing about susceptibility or resistence to allergic sensitization in this instance."

*We have quoted at length because these difficulties throw an interesting sidelight on the human where factors are much more complicated than in the experiment*

The patch test is the most important test in dermatology Substances which are suspect of giving rise to an eczematous reaction (plants, chemicals cosmetics etc.) may be applied to the skin and cause an eczematous reaction in the chosen site (as a rule the back).

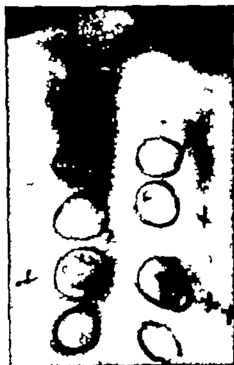
*Technique* A piece of cloth or several plies of gauze (about 1/2 centimeter length and width) is applied with the suspected substance. This piece is covered by a larger piece of impermeable tissue (*e g* cellophane) and the whole is well covered by adhesive plaster

The test is left in place 24–48 hours and read immediately after its removal and for several days afterwards

The concentration of the suspected substance should be neither so strong that it also causes a dermatitis in normal persons *(primary toxic action)* nor so weak that sensitive persons do not react. For the most usual substances this concentration has been determined empirically (see lists in SULZBERGER's and URBACH's textbooks) With a proper technique the patch test is a very reliable method though not infallible. *A negative patch test does not rule out clinical sensitivity as the actual circumstances of everyday contact are not imitated by the patch test* So a labourer may be sensitive to a given substance in his work (sweating, dust) while the patch test is negative. The skin is not equally sensitive

everywhere *e g* nail lacquer does not give rise to an eczema of the nailwalls as a rule, but it may affect the eyelids.

A positive patch test must also be controlled A patient may be sensitive to the vehicle used (*e g* petrolatum) Moreover an eczema



929 Patch tests made with insecticides being positive for ol. terebinthinae pyrethrum and pyrethrum in ol terebinthinae.

*(Simons–Amsterdam)*

patient may react to any stimulus by eczema (KÖBNER) (Polysensitization)

For industrial workers the so-called "*prophetic patch test*" is sometimes advised. It is performed by testing twice, with an interval of about a fortnight If the first test is negative and the second positive, a sensitization has taken place Its value is limited, however as a negative prophetic test does not rule out the possibility of subsequent

sensitization while a positive one does not preclude the frequent occurrence of "hardening" (i.e. spontaneous recovery)

Although much is unknown about the mechanism of the eczematous reaction, many interesting facts have come to light. Allergic contact dermatitis may be seen as an immuno-biological reaction where antibodies play a role. HAXTHAUSEN succeeded in transferring sensitivity from a sensitized to a non-sensitized animal by parabiosis. LANDSTEINER and CHASE transferred skin sensitivity to picryl chloride by washed cells of a peritoneal exudate (mainly lymphocytes). Although the next step-transfer of sensitivity from one individual to another by means of leukocytes of the circulating blood has not yet been performed (as has been done for tuberculin sensitivity by LAWRENCE) it is not impossible that a similar mechanism is involved here. Attempts at passive transfer in man (BEAR and others) by white cells have given dubious results.

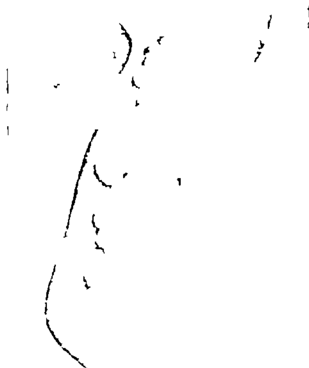
LANDSTEINER and CHASE demonstrated that the integrity of the lymphatics was essential for the establishment of sensitivity in guinea pigs. Although by no means proven, it is none the less probable that the epidermis and not the corium is the primary site of the eczematous reactions The sensitivity may be either highly specific (as e g in formaldehyde) or it may exist for a whole group of related substances (as e g cross sensitivity between sulphonamides synthetic anaesthetics and *para*phenylenediamine where the *para*-aminogroup is apparently the determining factor) Also the most simple chemical substances may give rise to sensitization (e g nickel) There is evidence to show that these simple substances combine with the body proteins to form complete antigens.

### II IMMEDIATE WHEAL REACTIONS (URTICARIAL)

An extract of the supposed allergenic substance (food or inhalant) is introduced into the organism by a superficial scratch (*scratch-test*) or by *intradermal injection* The intradermal test is the more sensitive, but should be used cautiously as dangerous general reactions with fatal outcome might be possible

The value of the immediate wheal-reactions is rather limited in dermatology At first sight one might think that they are of paramount interest in urticarial eruptions However experience has shown that

in urticaria they are not of much value. This is understandable if we assume that the urticarial reaction is not caused by the food as we know and test it, but by partly digested products Also in drug



930 Bullous allergic reaction to [illegible]bcutaneous injection of an extract made from rice bran in [illegible] p o w camp in order to fight vitamin-B deficiency

*(Simons Amsterdam)*

eruptions this test is almost invariably negative. In neurodermatitis (prurigo Besnier atopic dermatitis) the tests are sometimes found positive but often disagree with the clinical findings. Tests may be

positive, whereas the patient can take the incriminated food (or inhale the inhalant) with impunity On the other hand negative reactions do not exculpate any given substance. Some cases of urticaria and neurodermatitis have probably to be considered as non-allergic in origin. The same is true of strophulus infantum.

## PAPULAR REACTIONS (TUBERCULIN TYPE)

These well known reactions are of special interest for the diagnosis of many infectious diseases. They reach their maximum after 48 hours but may take longer (MITSUDA test in leprosy)

## INSECT BITES

Apart from toxic action (*e g* bee venom) reactions to insect bites may be due to an allergic reaction. This reaction may be of the immediate urticarial and/or of the delayed papular type. HECHT succeeded in passively transferring sensitivity of the first type and thereby demonstrated the presence of antibodies MELLANBY and HEILESEN adduced further experimental support to the view that the reaction to mosquito bites is of an allergic nature. (See Chapter 40) The reaction of different individuals to the same species of insects varies widely as is well known from everyday experience. Natural or acquired immunity is the rule for some species of insects, *e g* for the phlebotomus (DOSTROVSKY) Apiculturists as a rule become immune to bee stings, but some persons do not, and may react to repeated stings with fatal anaphylactic shock (JEX BLAKE). According to MELLANBY sensitization plays a role in the development of the clinical picture of scabies but HEILESEN could not confirm this view PRAKKEN and VAN VLOTEN have transferred passively (PRAUSNITZ KÜSTNER) antibodies from case of Norwegian scabies

## PLANT DERMATITIS

There are hundreds of plants which are known to have given rise to dermatitis This dermatitis is as a rule of the contact dermatitis type, and patch-tests may be applied in these cases

We shall mention separately some of the most important in the following categories flowers and plants, trees and weeds, and vegetables and fruit

#### FLOWERS AND PLANTS (Photo-phyto-sensitization)

Flowers may either act as sensitizers or have the characteristics of primary irritants.

The materia peccans may be found in the whole plant or only in parts thereof (bulb stalk, leaf). Some plant products are potent photo-sensitizers (*e g* lime-juice, oil of bergamot) "Meadow-grass dermatitis" (dermatitis bullosa striata pratensis) should be mentioned here. This dermatitis, which was first described by OPPENHEIM and FESSLER, is characterized by a vesicular eruption which is localized at the points of contact with the sensitizing plant. It has a streaky and rather "artificial" appearance. The eruption heals and leaves a long lasting pigmentation. Fig-dermatitis belongs to this class (CH. BERLIN, BEHDJET and PROSSER WHITE) Here the milky juice was proved to be the cause. Another mechanism is involved in the inflammations caused by cactus. If a spine enters the skin a pseudo-tubercle (corpus alienum) may be formed (WARTHIN and DAVIES) GLASS thinks that not the spines but the cactus juice causes the inflammation (*cf* copying pencils) A flower which should be mentioned is the chrysanthemum, as the insecticide pyrethrum is made from it Sensitizations are fairly frequent.

#### FRUITS AND VEGETABLES

Asparagus is a frequent cause of dermatitis The skin-sensitizing substance is localized in the stem only patch tests with other parts of the plant being negative

Citrus fruits can give rise to dermatitis, either by an allergic reaction to a volatile oil (URBACH) or by a primary toxic reaction (due to essential oils and other irritants) (SAGHER). Carrots can also produce an allergic dermatitis Allergy to tobacco is due as a rule to the added ingredients, rather than to the tobacco itself

#### TREES AND WEEDS

Many tropical woods can cause an allergic contact-dermatitis and the list of incriminated woods is so long that apparently almost any tree may act as an allergen.

The most important are according to SENEAR aroeira, Borneo rose wood, box wood Brazilian walnut, cocobolo coco-wood, ebony

positive whereas the patient can take the incriminated food (or inhale the inhalant) with impunity On the other hand negative reactions do not exculpate any given substance. Some cases of urticaria and neurodermatitis have probably to be considered as non allergic in origin. The same is true of strophulus infantum.

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Pyrethrum, which is not infrequently pathogenic, has already been mentioned (see flowers)

SIMONS and JANTZEN have drawn attention to the fact that the term of flit-dermatitis is often incorrectly applied to eczema from other similar products.

*Clothes* may also be the cause of dermatitis especially woollen and silk clothes. Sweating is a predisposing factor

*Shoes* may also cause a dermatitis (allergic or non-allergic) due either to the leather or to one of the many products used in the finishing process Sweating is a predisposing factor here, as it is in the frequently seen dermatitis under watch-straps. In this latter dermatitis (from leather, plastic or metal straps) the accumulation and stagnation of sweat may be the provoking factor Allergy to drugs does not differ essentially from drug allergy in temperate climates and the reader may be referred to one of the textbooks on allergy However photo-sensitization (sulphonamides!) is more important in the tropics.

### ALLERGIC DERMATOSES

The most extensively investigated and important form is contact dermatitis. The aetiology has been discussed under the patch test. Eliciting factors have already been discussed.

Other forms of eczema (eczema from within) are a rather heterogeneous group Further study may tend to make changes in our classification.

Neurodermatitis (prurigo Besnier atopic dermatitis) may be, but is not always of allergic origin. The skin does not, as a rule, react to epidermally applied allergens (patch test) but only to cutaneously applied ones The tests often do not correspond to the clinical picture There are probably not a few cases which are non-allergic in origin. The psycho-somatic approach is one of the later developments

### URTICARIA

Urticaria is often caused by food. Elimination tests are the most practicable though difficult way of elucidating the cause, as the skin-tests are usually disappointing Apart from foods intestinal parasites, drugs, autogenous products (focal infection) and inhalants (feathers, pollen)

external substances may also cause urticarial reactions e g contact with lemon peel (URBACH) The urticaria after nettle stings (urtica urens) or insect bites is not due to contact but to an "intracutaneous injection Physical influences (heat cold) intestinal disorders and psychic excitement may also give rise to hives. Probably many cases of urticaria are of a non-allergic nature.

## PROPHYLAXIS AND THERAPY

In those cases in which the allergen is known, avoidance is the logical prophylaxis. In many cases this will not be practicable, and other steps have to be taken. For industrial dermatoses protective creams have been compounded (SCHWARZ, PECK and TULIPAN) The use of so-called "soapless soap instead of ordinary alkaline soap is strongly recommended If a dermatitis or an urticaria has developed, ordinary dermatologic therapy should be instituted. It must not be forgotten that every pathological process is the result of an interplay of many known and mostly unknown factors General measures which ensure a state of health as perfect as possible mentally and physically are of paramount importance. Probably many cures have to be attributed to the hope and confidence given the patient through a prescription, rather than to the pharmacological action of the ingredients Especially in cases of chronic urticaria and neurodermatitis the psychic factor should not be neglected.

Specific measures against allergic processes are injection of the allergenic substances in minute, increasing amounts. It is probable that the blocking antibody' (COOKE, LOVELESS) plays a role in the therapeutic efficacy but proof is lacking Extracts should be made (if possible aqueous) and weekly injections should be given in increasing doses. Oral desensitization has been advised especially for poison ivy (C. MENSE) but its value has been doubted.

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# JUNGLE DERMATITIS

## (Dermatoses caused by tropical plants and woods)*

R. D. G. PH. SIMONS

Amsterdam

A number of substances have become notorious in the tropics. We mentioned a few of these in passing when dealing with eczema, dermatites forestières and lucites, because light is an important factor in the genesis of certain allergic eczemas. A clear distinction should be made between *dermatites forestières* and *phyto-photo-dermatoses* as was already explained in Chapter 1 (p. 66–70 and 90–100).

The undermentioned substances (for convenience's sake arranged alphabetically) should still be mentioned in this connection.

*Agave* (one of the Narcissus group) is the American aloe or century plant which is said to flower once in a hundred years. It grows also in the tropics. "Agave dermatitis" resembles more or less the—better known—"ragweed dermatitis".

*Anacardiaceae*. These, together with the euphorbiaceae, are surely the most notorious plants. *Poison ivy* (Rhus toxicodendron) is the best known representative of this group. In the tropics, however, *poison sumac* (Rhus vernicifera, which is used in the manufacture of Japanese lacquer), *Jamaica* or *coral sumac* (Rhus metopion) and *cashew nut* (Anacardia occidentalis) play a greater part. Rhus vernificera, which contains urushiol, may cause urticaria and eczema in persons working with Japanese lacquer. Jamaica sumac, also called mountain manchineel (see euphorbiaceae) contains the irritant named cardol.

The cashew nut is called, in Indonesia, *katjang monjet*, *i.e.* ape nut. The sap, both of the leaves, of the bark and of the fruit, contains

* See also Chapter 1 pages 66–70 and 90–100.

anacardol and may set up bullous dermatitis. The nut itself which is eaten as an accompaniment to the apéritif is harmless It is important to know that the sap of the cashew nut turns black when exposed to the air for which reason it is sometimes used as marking ink, when textiles so marked may set up anacardol dermatitis The same applies to the marking ink nut (Semecarpus anacardium)

A well-known plant in the tropics is the *manga* *i.e.* Magnifera indica. Peeling the fruit with the teeth or sucking up the flesh of the fruit previously beaten to a jelly through a hole in the rind, might set up circumoral dermatitis Cheiropompholyx, too is frequently blamed on to manga-eating this opinion, however is probably incorrect. It is more likely that cheiropompholyx, which both in the tropics and in Europe, is more or less a seasonal disease, occurs predominantly during that part of the year when the manga fruit ripens. (See also renghas)

*Ananas* (Pineapple) Genuine pineapple eczema is rare, and, in fact, far from well-known. What is called "*pineapple estate pyosis*" is probably caused by an acarus, as, for instance, is also the case with *copra itch*

*Bamboo* SCHIFF has reported a vesicular dermatitis resulting in pigmentation in a bamboo sander (*Arch Derm and Syph* 1951). Sometimes the condition is not due to the bamboo itself but to fungi living on the bamboo, *i.e.* the Arundaria alpina (BEQUAERT–Central Africa) BENGEL (*Arch Dermat and Syph* 1951) described dermatitis from bamboo rackets (varnish?) Most cases of bamboo dermatitis should in fact be attributed to the varnish if not to insects

*Banana dermatitis* from the banana fruit (Musa sapientum) is extremely rare, and when it is suspected to be present one should still think of other agents According to SCHWARTZ, TULIPAN and PECK the pulp and rind contain different sensitizing agents. They draw attention to the fact that insecticides on the banana tree may account for so-called banana-dermatitis

*Batata-itch* is usually due to the batata louse In Surinam, the "*patatta luso* *i.e.* the larva of Trombiculum flui and T vanommereni is found in the grass Together with T helleri (absent, or very rare, in Surinam) it belongs to the T batatas group (LINNAEUS) *i.e.* T flui. BRUMPT distinguishes between Leptus batatas the "bête rouge" of

the Antilles and T. flui and T. vanommereni. The batata louse is also found on chickens and lizards. It is open to question whether it infests precisely (and exclusively) the batata plant, a supposition which, indeed, was contradicted by BONNE. VAN THIEL and VAN OSDIEREN on the other hand, found the T. flui in the so-called "garter plants" (leguminous Vigna sinensis); these authors assume that the name "batata louse" derives from the fact that the insect for preference attacks whites (whose nickname is "pataten").

*Bay-rum* is an alcoholic perfume distilled from the leaves of Amomis caryophyllata, and widely used in South America. Its counterparts are eau de Cologne and Cajeput oil (Far East) mentioned below. It may cause dermatitis and breloque dermatitis.

*Betel nut.* The *betel nut* is used in Indonesia for sirih-chewing, which stains the mouth red. It is said that the nut and the leaves of the betel-pinang or Areca catechu palm have a refreshing effect and cause a slight "nitritoid" complexion. This habit may eventually cause oral carcinoma.

*Cajeput oil* is very popular in SOUTH ASIA since it is used for massage, thus often causing dermatitis and/or folliculitis. Cajeput oil originates from the eucalyptus tree and is also used as a perfume in ointments, just like wintergreen oil. (See obat matjam.)

*Cannabis indica* or *henna*. Henna is known as a hair dye. The majority of hair-dye eczemas, however, are not due to henna but to other substances. It is even worth considering whether in such cases, it would not be better to use henna in future, as it relatively rarely causes eczema. (See also bay rum.)

*Chrysanthemums.* Of the different species of chrysanthemums, pyrethrum is the best known. It is dealt with in more detail under the insecticides.

*Cinnamon.* Cinnamon dermatitis following direct contact with cinnamon as well as pruritus following ingestion of cinnamon has very rarely been reported. LEIFER (*Arch. Derm. and Syph.* 1951) reported a case due to toothpaste, although the tongue and lips were not affected. He compared this case with JADASSOHN'S case of iodoform dermatitis by the application of vaginal tampons by which the vulva was not affected.

*Citrus* The active component in the bark, limonene, is a terpene The peel contains citral geraniol, etc. which may both cause eczema and photosensitize the skin. (Circumoral pigmentation may result from peeling the citrus fruit with the teeth.) *Citronella*, which is applied to the skin to ward off mosquitoes, may also set up eczema. To this group also belongs *bergamot oil*, a component of eau de Cologne and other lotions. Bergamot oil may have a strongly photosensitizing action on the skin, for which reason one should be seriously advised against cooling the face by dabbing it with eau de Cologne. Figure 96 in Volume I shows a bullous dermatitis above the pigmented streak, caused by an experimental bergamot oil dermatitis. Hair lotion containing bergamot oil may cause pigmented streaks in the neck, sharply delimited against the edge of the blouse or collar Figure 91 in Volume I shows a hair lotion dermatitis of the hand of a woman who had washed her hair As can be plainly seen, the skin under the finger ring which had got wet but was protected against the sun s rays remained unchanged. Histological examination showed that the corneal layer was dark in colour but no increased pigmentation could be found.

Of the different species of citrus fruit the grape fruit is also and particularly the cause of dermatitis and discoloration. We once had, in a P O W camp an "epidemic" of a capricious looking pigmentation of the abdominal skin in a number of prisoners of war It turned out that this was caused by the men tearing the fruit open above their naked belly (they wore very few clothes) and letting the sap from the peel flow and spatter abundantly over the skin. (See SAMS and ALDICK s articles on this subject in the *Arch Derm and Syph* 1941 and *Der Hautarzt* 1952.)

*Caoutchouc* Dermatitis from natural or synthetic India rubber is almost always due to the accelerators used for vulcanization, the most notorious being mercapto-benzothiazole. (See latex.)

*Copra itch* As already mentioned in Chapter 1 copra itch is not, in fact, an allergic eczema, but is caused by Tyroglyphi and similar acarids Figs 52 and 53 in Volume I

*Cotton seed dermatitis* also called SCHAMBERG s disease, is a similar zoonosis as copra-itch. (See Chapter 1 (zoonoses).)

*DDT* (dichlordiphenyltrichlorethane) which is widely used on

the plantations causes relatively little dermatitis and even then one should inquire whether the dermatitis was not, in effect, caused by the substance mixed with the DDT

*Djatti* (from the wood of Tecona grandis) This is dealt with under teak wood.

*Euphorbiaceae* To this group belong, among others, *Hippomane mancinella* or bdingamosa (meaning "quarrelsome woman") of the Antilles the *arbre aveuglant* (Excoecaria agallocha) the *castor oil plant* (Ricinus communis) and the *poison tree* (in Surinam, possentree) or Hura crepitans. The sawdust of these trees is sufficient to cause an allergic eczema. How strong the stimulating action of the sap is, may be clear from the name "arbre aveuglant" (= blinding tree) As regards the ricinus seeds we were told that they were used by exiled criminals in French Guiana for the purpose of provoking dermatitis, so as to get exemption from hard labour The poison tree, which contains hurine is supposed to be able to cause a dermatitis resembling erysipelas.

*Figs* The sap of the Ficus carica plant may set up eczema and blisters and also sensitize the skin to light, thus causing a "pigmentation" of long duration. Packers of preserved figs may reveal dermatitis due to the juice as well as dermatitis from the preserving material.

*Grasses* may irritate the skin and may cause pruritus and eczema or pyoderma. This is usually due to stinging hairs, as is the case with the Melinis minutiflora and Andropogon rufus. Many cases of grass dermatitis however are actually caused by chiggers.

*Insecticides* The majority of the large number of existing insecticides consist of a mixture of different substances nearly all of which may themselves, act as a stimulus and set up an allergic dermatitis.

*Derris* (powder from the root of Derris elliptica) and *pyrethrum* are sprinkled about or burned as incense *(obat njamuk)*

The *derris* only rarely provokes an allergic eczema. In a number of workers in a derris factory however we found, in addition to laryngitis caused by inhaling derris powder also eczema of the scrotum. Most probably this was caused by derris powder adhering to the men's trousers A number of men, moreover, had conjunctivitis In ordinary daily life *i.e.* outside the factories, derris eczema practically never occurs. To the derris group (*i.e.* the Lonchocarpus, one of the Papil-

lionaceae) belongs also the *arkau-* or *cube-root* which is used in South America as fish-poison. Its active components are rotenone and "derris ether-extract" each of which is also used separately as an insecticide.

Of *pyrethrum* the best known are Chrysanthemum pyrethrum and Pyrethrum cinerariifolium. Of these two it is the flowers that are most generally used this in contrast to the pyrethrum listed in the Pharmacopoeia, which is made from the roots of Anacyclus pyrethrum. Mixed with citronella, cajeput oil, paraffin oil, arsenic, naphthalene, etc., the various insecticides are put on the market under different names. All these remedies must satisfy at least five conditions (1) they must kill insects, (2) they must not cause any stains (3) they must not have a bad smell, (4) they must not provoke eczema in either man or animals, and (5) they must not be inflammable.

*Jute dermatitis* and folliculitis due to several species of the Corchorus plant occur when the material is prepared with potassium hydroxide and oils and dyed. The jute dust may cause bronchitis.

*Kajeputh oil* – see Cajeput oil.

*Katjang or Dam Gattel* This plant, the "itch bean or "itch leaf" is Mucuna pruriens ("cow-itch") It is one of the Fabaceae.

*Lapacho wood* or Tecoma avellanedae may cause eczema and blisters, as has been reported by CORDERO and LYNCH in the *Prensa med. Argentina* of 1951

*Latex* In the P O W camps in the midst of the rubber woods, the substance used to stick everything together was latex, the milky viscous fluid tapped from rubber trees. It was used especially as adhesive to attach gauze to the skin for the protection and treatment of wounds and ulcers Out of thousands of cases thus treated we never once saw a single one of dermatitis, although the latex might occasionally cause slight folliculitis or a little erythema when pulled away from the skin. In Mexico the so-called *guayule dermatitis* is attributed to the latex of Parthenium argentatum.

*Lemons* See Citrus.

*Mahogany* The beautiful wood of this representative of the Meliaceae contains chloroxylonine which in some cases may provoke eczema. The fresh wood may colour the skin a reddish brown.

*Mango*. See Anacardiaceae

*Obat Matjam* the famous "*tiger balsam*" the panacea of South-East Asia, probably contains cajeput oil, camphor and wintergreen oil (salicylus methylicus) In a certain number of cases it provokes dermatitis

*Oranges* See citrus.

*Orchids* See vanilla.

*Parsnips* After my statements in Volume I page 92 that the parsnip (pastinaca) does not grow wild in Indonesia and that there, instead of the Umbliferes, especially the Rutaceae including the citrus, may cause a meadow-dermatitis (dermatitis pratensis) BELISARIO has reported parsnip dermatitis in the *Australian Journal of Dermatology* of 1952. The condition was seen in a group of men who had peeled parsnips being at the same time exposed to sunlight. The lesions were suggestive of mustard gas contamination and even of self-induced lesions. CHALMERS and PEKKOLA have described a Rutacea-dermatitis in the Sudan, due to Halophyllum tuberculatum and which was accompanied by facial oedema. (See also footnote page 94)

*Pineapple itch* or *pineapple estate pyosis* See Ananas

*Ragweed* (Ambrosia artemisifolia or—elatior) is a common field weed with lobed leaves Its pollen and plant juice are said to cause dermatitis.

*Renghas* Gluta renghas is one of the Anacardiaceae referred to above. The dermatitis it causes may be so serious that it is sometimes called renghas pemphigus in Indonesia. Fig 50 in Volume I

*Rottan* Rottan dermatitis" revealing wheals, papules and a kind of prurigo nodularis is not, as a rule, caused by the rottan but either by the varnish or by the rottan mite. In most cases the latter turns out to be the common bed bug, which scampers into the smallest hiding places One should therefore not give immediate credence to a patient's statement that there are no bed bugs in his rottan chairs! (Fig 54 and 53 in Volume I)

In a large number of cases, the bed bugs hide in the cane chairs the moment one rises they speedily retire again.

*Rubber* Eczema, either local or widespread, due to vulcanized rubber or to elastic (garters, artificial teeth, etc.) is relatively frequent (see also under latex and caoutchouc). Leukoderma from contact with

rubber has been reported by OLIVER *et al* (*J.A.M.A.*, 1939) and SPENCER, DOWNING, and others (*Arch Derm and Syph.*, 1948 1952)

*Sadd* or *Sett dermatitis* is a papular eruption due to contact with the panicum pyramidale plant in the river Nile.

*Sisal dermatitis* is usually due to the lactic acid or other sensitizing agents of the juice.

*Soaps* Since residents of the tropics go in for much washing and bathing every soap manufacturer tries to put a product on the market which is still more "medical" than that of his competitors, the chief means to this end being the addition of carbolic acid, sulphur, coal tar, etc. The majority of these "medicaments" have little value. A number of them provoke eczema, to cure which the patient then bathes with still greater zeal—using the medical soap In investigating soap-allergy one should especially bear in mind what SULZBERGER and BEAR write in FISHBEIN's 'Medical Uses of Soap" "The demonstration of true allergic sensitivity to an ingredient of a soap is rendered difficult if not impossible by the fact that the application of soap solutions in skin tests invariably includes not only the application of the potential allergenic ingredients, but also applications of dissociated alkali and acid as well"

*Sugar* On the sugar plantations themselves there is practically no sugarcane eczema but in the sugar mills scaly and tylotic eczema of the palms, sometimes coupled with hyperkeratosis of the nails is often found in women whose work it is to scrape the centrifuges, and who use large quantities of water What is called "*sugar furunculosis*" and tendosynovitis falls outside the scope of the present chapter

*Tobacco* In common with the tomato and the potato the tobacco plant belongs to the Solanaceae Tobacco eczema is not, as a rule, caused by the leaves, but by preservatives, insecticides or "flavours" such as vanilla. Cigarette smoker's pharyngitis should, perhaps, be attributed to the glycerine with which the cigarettes are treated, rather than to the tobacco

*Tea* It is probable that "*tea dermatosis*" is no more an allergic eczema than is copra itch, but an epizoonosis caused by the bite of Rhizoglyphus parasiticus

*Teakwood* One species of which is djatti (Indonesia) and iroko (African teakwood) may in some cases provoke an allergic eczema.

This eczema is sometimes difficult to recognize as such, because the processing of older wood may also cause eczema.

*Vanilla* dermatitis usually occurs through the juice of the pods, when not from acari or from the alcohol and cashew nut's cardol, which may be used to preserve the pods. Vanilla plantifolia is the most common vanilla of the orchidaceae.

*Vesicant insects*" are numerous in tropical forests Most notorious are the coleopterae and lepidopterae. The canthardes of the meloides group and the staphylinideae (amongst which the dangerous paederus) belong to the coleopterae. Except urticaria some of these insects may cause convulsions vomiting and dyspnoea.

The browntail Euproctus crysorrhoea moth may cause moth dermatitis by its hairs. VINCENTE reported moth dermatitis in Venezuela from a hylesia moth belonging to the family Saturnideae (*Acta cientif Venez* 1952). See Chapters 34 to 40.

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# CHAPTER 91

# DRUG ERUPTIONS IN THE TROPICS

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In hot countries, rashes due to the absorption of drugs tend to occur even more frequently than in temperate zones. There are three main reasons for this — the exposure of the skin to strong sunlight, increased sweating leading to excretion of drugs via the skin, and the use of drugs administered particularly for tropical diseases. The eruptions tend to be of a more severe nature than in colder climates and tend to take longer to disappear.

As details concerning drug rashes can be found in any large modern textbook on dermatology, this chapter concerns itself chiefly with those which are more likely to occur in warm climates.[1]

## 1 *Quinine and its derivatives*

These fortunately do not often produce rashes. The characteristic quinine eruption is a scarlatiniform erythema, followed by desquamation. This can be readily mistaken for scarlet fever or recurrent scarlatiniform eruption. Sometimes purpuric, urticarial or vesicobullous forms occur, but more common than these is a kind resembling contact dermatitis, when the skin of the patient has been sensitized by previous local application of some quinine application, *e.g.* the scalp following the use of a quinine "hair tonic", or the penis, from quinine

[1] See [illegible] Figs 35, 48, 49 in Vol[illegible] 1

pessaries (Fig 932) Ingestion of the drug is followed by a weeping erythematous eczema on the areas sensitized.



931 Pigmentation of the lips due to quinine.
*(Dodds–London)*

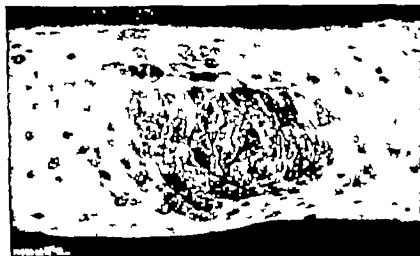


932 Contact dermatitis type of drug rash due to quinine.
*(Dodds London)*

The long-continued ingestion of quinine can occasionally produce a deep brown pigmentation, particularly of the buccal mucous mem-

brane, the glans penis, and sometimes of the lower limbs, and it should be borne in mind that quinine is one of the chemicals which can produce fixed drug eruption.

Usually those intolerant of quinine are able to take related drugs such as pamaquin though these too may infrequently produce side effects. *Chloroquin* produced a lichen planus-like eruption in two patients, according to ALVING and others and among other toxic symptoms pruritus is mentioned by HAWKING



933 Psoriasiform quininoderma (perhaps acute psoriasis) within one week's time following tentamen aborti with 30 tablets of quinine in a 40-year old woman, who had not suffered from psoriasis previously. The face was also affected.

*(Simons–Amsterdam)*

## 2. *Mepacrine (Atabrine Quinacrine)*

In pre war days it was known that this drug could produce exfoliative dermatitis, as well as the characteristic yellow pigmentation of the skin, and references to this dermatitis could be found in textbooks such as BECKER and OBERMAYER and ANDREWS. During the 1939—1945 war however many patients were seen affected by a bizarre eruption sometimes called for convenience *tropical lichenoid dermatitis*

Cases were reported independently from the Pacific by BAGBY NISBET and others from the Mediterranean by NELSON and PETERKIN and HAIR, DOSTROVSKY and SAGHER and from India by BIGHAM and others. (See page 64 Vol. I)

The primary lesions of this drug eruption frequently appear on areas traumatised by a previous dermatosis and in some patients the earliest sign is a dry fissured hyperkeratosis of the palms or soles, or small dusky purple nodules usually on the feet or hands. The rash may appear within a week of taking the drug or may appear after months of its ingestions. Within seven to fourteen days of the primary rash, an eczematoid type of dermatosis appears on the limbs and trunk,



934 Mepacrine drug eruption showing purple pityriasis rosea-like plaques and follicular hyperkeratosis.

not unlike a pityriasis rosea. On these patches soon develop indurated plaques 1 cm to 10 cm in diameter dark violet in colour and leaving an intense black pigmentation on cessation of the drug These curious patches are topped by a dry white scale and have sites of predilection — the necklace area costal margins, inner surfaces of the thighs. Profuse dandruff and crusting of the chin, ears, eyebrows are not uncommon, while some patients develop atrophic bald patches resembling lichen plano-pilaris (For alopecia see page 46 Vol. I).

DOSTROVSKY and SAGHER have reported annular lesions, which were especially located on the forehead, extremities and mucosae of the mouth and genitalia. Exposure to sunlight provoked the

eruption. Histology of the lesions was not distinguishable from that of lichen planus

*Oral lesions* are usually present, sometimes as bullae or ulcers, some-



935 Mepacrine eruption: affection of a tooth

times as cheilitis and angular stomatitis sometimes as white areas indistinguishable from lichen planus.

Once the drug is discontinued, a gradual spontaneous recovery



936 Gold dermatitis, lichenoid type

*(MacKenna–London)*

ensues, but residual scarring and a tendency to relapse may remain.

A somewhat different form of mepacrine eruption can occur either independently or at the same time as the other. This consists of a deep

This curious phenomenon has been published in the *Brit J Dermatol and Syphilol.*, 61 (1949) 287

pigmentation of the gums hard palate, nailbeds and cartilage of the nose, and has been described by several authors including WILSON and LUTTERLOH and SHALLENBERGER. In a case described by PETERKIN a tooth was affected (Fig 935) HERMANN and MILLER published an exhaustive paper on the pharmacologic effect of mepacrine on the skin.

### 3 *Heavy Metals*

These include *gold, arsenic bismuth mercury* and *antimony* all of which can produce varied types of drug eruption. These are nowadays



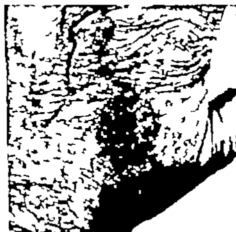
937 Morbilliform sulphonamide eruption *(Dodds–London)*

938. Lichen planus eruption due to neoarsphenamine. *(Zoon–Utrecht)*

usually given by injection and can produce rashes which can simulate almost any skin disease. Reactions may be eczematous, morbilliform, scarlatiniform, purpuric, vesicular or bullous, or may resemble seborrhoeic dermatitis, erythema multiforme, or lichen planus Exfoliative dermatitis is not uncommon, and responds well to BAL injections as does the lichenoid type which resembles a mepacrine rash (Fig 936) RITTEY described an exfoliative dermatitis due to antimony used for bilharzia, with an excellent response to BAL. According to WATSON *Viledin (Miracil D)* can produce tingling of the skin among other toxic effects

4 *Sulphonamides*

The especial danger in the administration of the sulphonamides in hot countries is the great tendency for the skin to become photosensitive and to remain so for months or years. Sulphonamide photo dermatitis is by far the most common form of sensitivity to these drugs and, though generally induced by sulphathiazole, sulphanilamide or sulphapyridine, can also be caused by less toxic ones such as sulphaguanidine, phthalylsulphathiazole and sulphasuxidine. The severity of this condition can vary from a mild maroon-coloured papular rash affecting areas exposed to sunlight to a generalised exfoliative derma-



939 Fixed sulphonamide eruption.
*(Dodds–London)*

titis. The most frequent type is the one which produces a crusted weeping dermatosis of the face and neck and a vesicobullous eruption of the hands. It can be readily distinguished from a severe seborrhoeic dermatitis by the conjunctivitis, cheilitis and involvement of the skin of the nose and sides of the neck (Fig 940).

The sulphonamides can cause many other types of rash — urticarial, morbilliform (Fig 937) scarlatiniform, purpuric, pemphigoid vesicular and pustular — and may simulate such diseases as lupus erythematosus erythema multiforme and erythema nodosum. Infrequently a fixed

drug eruption is observed and is liable to occur as bullous lesions on the buccal mucous membrane or the glans penis. As the bullae disappear, a dusky red patch can be seen which is followed by pigmentation (Fig 939).

5 *Antibiotics*

(a) *Penicillin* sensitivity can show itself in many ways, the most common being in the form of a giant urticaria often accompanied by joint pains Other reactions include erythematopapular and vesicular rashes erythema nodosum a red oedematous swelling around the site of the injection an eruption closely resembling sulphonamide photo



940 Acute sulphonamide dermatitis
*(Simons—Amsterdam)*

dermatitis and the awakening of a dormant fungous infection, especially of the hands, feet and groins, first described by FEINBERG It must not be forgotten that if procaine penicillin is used, the procaine can produce an eczematous reaction also

(b) *Streptomycin* is the antibiotic most liable to produce skin reactions These are most commonly seen in the form of contact dermatitis of the hands and face in nurses giving the injections, but drug rashes are often encountered STEINER and FISHBURN have described roseolar urticarial morbilliform- scarlatiniform, follicular and erythema multiforme-like exanthems, while in Malaya PALLISTER observed the death of two patients with exfoliative dermatitis and stomatitis during streptomycin treatment (See Chapter 65 )

(c) *Aureomycin* and *Chloramphenicol* (chloromycetin) therapy may be followed by the development of yeast infections, notably around the mouth and anus, but drug eruptions are by no means unknown. Probably the most frequent is a mild generalized desquamation, but erythema nodosum can be produced and sulphonamide photo dermatitis can be reactivated. PECK and FELDMAN record urticaria and erythema multiforme following its use. (See Chapter 65.)

6. *Barbiturates*

So many drugs of the barbiturate group are being prescribed that it is no wonder that eruptions due to them are becoming more frequent.



941 Ringwormlike phenobarbitone rash on the forearm.

The commonest type is a widespread morbilliform rash, but fixed drug eruptions urticarial, scarlatiniform varieties are seen. One has also observed erythema multiforme, and very occasionally STEVENS-JOHNSON disease. A characteristic one is a haemorrhagic bullous eruption localized on the dorsa of the hands (Fig. 942). There is one type which is provoked by exposure to sunlight and occurs on exposed areas such as the cheeks and neck as dusky red circinate patches with a scaly edge, not unlike lupus erythematosus (Fig. 943).

## 7 Sulphones

With the introduction of sulphone therapy for leprosy new hope has arisen in the breasts of those afflicted, but it must be remembered that these drugs are powerful ones and side-effects not infrequent. WOLCOTT has drawn attention to the phenomenon named erythema nodosum leprosum and has observed that 93% of these occur after treatment. He considers that its presence indicates increasing resistance to the disease and has found that fuadin, a trivalent antimony compound, given by injection relieves the symptoms. These reactions can



942. Haemorrhagic bullous eruption due to barbiturates.

be provoked by all sulphones such as diaminodiphenylsulphone, promin, diasone and sulphetrone, according to COCHRANE. The same author (personal communication) says that aqueous sulphetrone produces no toxic reaction of note except for a dermatitis which sometimes goes on to an exfoliative one, though occasionally an urticaria is seen. GARRETT reporting the administration of Dapsone to over 9 000 patients mentions that the incidence of dermatitis is about 3% The early symptoms of this were fever and pruritus, followed by a rash not unlike "prickly heat" In some cases exfoliative dermatitis developed and death occurred in four patients.[1]

[1] See also pseudo lepra reaction p 513 Vol I

### 8 *Germanin (Suramin Bayer 205 Antrypol)*

This drug is employed in the treatment of trypanosomiasis as well as other diseases, and can produce toxic effects including an eczematous dermatitis which may develop into an exfoliative dermatitis and lead to the death of the patient.

### 9 *Hetrazan (Banocide)*

In seventeen cases of loasis treated by MURGATROYD and WOODRUFF only five had no cutaneous reactions. On the day after treatment six complained of itching and in three of these rashes appeared one was



943. Barbiturate rash resembling lupus erythematosus.
*(Dodds-London)*

morbilliform, one urticarial and one erythemato-papular and all lasted only 48 hours. The itching which in all but one lasted only three to four days was relieved by antihistamines. In three others, small cutaneous nodules which disappeared in three days were noticed, and in three more there occurred linear swellings, from two of which dead adult *L. loa* were extracted.

In cases of filariasis and onchocerciasis treated by HAWKING and LAURIE, patients with *W. bancrofti* had on occasions tender spots on the groin and scrotum. Onchocerca cases, however had a violent

reaction lasting for sixteen hours. The skin, especially of the thighs and buttocks, was tender and swollen, and sometimes there was oedema of the prepuce, penis and scrotum. An intense widespread itchy rash on the trunk and limbs was also observed

**THERAPY**

The first essential in treatment of dermatitis medicamentosa is to stop the offending drug and in fact to avoid all drugs which are not strictly necessary since related chemicals can readily reactivate the condition. For instance, a sulphonamide dermatitis can be reproduced by the application of acriflavine or by the injection of procaine, and aureo-



944 Fixed drug eruption due to phenolphthalein. Deeply pigmented plaque on the right knee

mycin given by mouth can light up a contact dermatitis originally due to penicillin (NILSON — personal communication) In the average acute case, cessation of the drug is followed by disappearance of the rash within a few days, *e.g.* the morbilliform one caused by sulphonamides or barbiturates Sometimes however, drug eruptions do not vanish for months and may leave permanent destruction of the skin, as in the severe cases due to mepacrine or the heavy metals. In those who have had a sulphonamide photo dermatitis, photosensitivity may

persist for months or years and these patients are often subject to low-grade septic infections.

*Local treatment* depends entirely on the type of the eruption. The urticarial, morbilliform, scarlatiniform or erythemato-papular one is best treated with a soothing lotion such as 2% ichthammol in calamine lotion, dabbed on freely several times daily. Eczematous and exudative dermatoses are suited by wet dressings of ¼ % silver nitrate, Burow's solution, 1 : 5000 potassium permanganate, and similar preparations. Ointments, water miscible creams, and thin pastes are contra indicated in hot climates but Lassar's paste in the form of spreads often does well. To this can be added an antiseptic such as 1% ammoniated mercury if sepsis is present.

*General treatment* In the average case, rest in bed is essential. Many patients who develop drug rashes appear to be constipated, and brisk purgation is a valuable aid in treatment. The diet should be nourishing light, and non-stimulating, and plenty of fluids should be insisted on. In some cases, massive doses of vitamins are to be recommended, particularly A and D, B complex and C. For instance vitamins A and D and B complex seem to be of value in gold and mepacrine eruptions, while nicotinamide 50 mg daily by injection reduces photosensitivity in sulphonamide rashes. Crude liver injections sometimes appear to exert a beneficial influence.

The effect of the antihistamines is often disappointing, but they are indicated in dermatoses where there is a marked urticarial or erythematous reaction. Penicillin urticaria can usually be controlled by high dosage, but sometimes responds better to injections of adrenaline. Antihistamines are also recommended for the dermatitis which results from sulphone therapy and for those reactions which occur with the administration of Hetrazan.

Dermatitis due to the heavy metals is often persistent and refractory to treatment, though early use of BAL will sometimes but not invariably shorten the illness. BAL appears to be helpful in any such metallic poisoning and is given by intramuscular injection, in a dosage of 3 mg per kilogram of bodyweight in severe cases. It should be administered in hospital, as toxic effects are not uncommon.

For patients who are seriously ill and toxic, a blood transfusion

often works wonders, and plasma or saline intravenously are also valuable on occasions.

Light sensitive patients, especially those with sulphonamide eruptions, should be nursed in a dimly lit room and exposed very gradually to direct sunlight. Parasol creams can be used, but *para*-aminobenzoic acid should be avoided, owing to its close chemical relation to the sulphonamides (2—10). Tannic acid is as effective as any other sun-protective.

In some cases of drug eruption, like the severe ones due to mepacrine, heavy metals and the sulphonamides, secondary sepsis may constitute a difficult therapeutic problem, and it may be necessary to prescribe penicillin or aureomycin with due caution.

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# THE CONCEPT OF "IDS"

## (Introductory remarks on its nature and value)

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In the medical terminology of infectious diseases the suffix "*osis*" generally denotes "*disease-entity*" *i.e.* a complex of signs and symptoms due to a particular infectious agent (tuberculosis, trichophytosis, oidiomycosis, etc.).

Under each of these designations there are included *all* the often variegated pathologic phenomena directly or indirectly produced by the micro-organism concerned.

Among these different phenomena there are the characteristic primary or original lesions occurring at and about the site of first inoculation — *e.g.* the chancre of syphilis, the primary complex of tuberculosis, the primary granulomas, in the scalp or bearded area etc., of deep trichophytosis etc. Sometimes subsequent to these "primary" alterations, it is not uncommon for certain infections to give rise to "secondary" manifestations, distant from the primary complex and differing from it in many essentials. These "secondaries" can appear while the primary lesions at the inoculation site are still active, or anytime later, even long after the primary lesions have healed and vanished.

The characteristic sequence: "primary-complex, secondary lesions" is not found in all infectious diseases but is prone to occur particularly in those infections in which the micro-organisms act by producing tissue-sensitizing *allergens* rather than by elaborating intrinsically cell-damaging *toxins*. In these *tissue-sensitizing infections* the following sequence is characteristically demonstrable:

1. The invading micro-organism penetrates the virginal, never previously exposed, not yet sensitized tissue.

2. The micro-organism multiplies, produces sensitizing allergens, and creates a state of specific hypersensitivity both at the inoculation site and distant therefrom.

3. At the end of a given and characteristic incubation period, when the quantity of microbic allergens has sufficiently increased and the local tissue sensitivity has reached a sufficient level, the interaction between microbic allergens and sensitized tissue gives rise to the first clinical manifestations of the primary lesion.

It will be seen that in this series of events in the pathogenesis of the primary lesion the inoculated tissue is *non-sensitive* at the time the micro-organism first arrives and there is an ensuing nascence and growth of tissue sensitivity concomitant with the growth and waxing of microbic allergens.

In the pathogenesis of the secondary and later lesions the conditions are radically different.

1. The micro-organisms and/or their allergens are disseminated from the primary focus or foci and arrive at more or less distant sites, in a tissue which, due to the preceding primary infection, is *already* specifically altered in its capacity to react, already specifically sensitized and immunologically conditioned.

2. There is therefore no need for an "incubation period" during which the specific sensitivity is born and develops in degree.

3. These facts of already established specific immunologic tissue alterations *preceding* the arrival of the infectious agent or allergens, modify the appearance, course, duration, extent, prognosis and other features of the secondary and later lesions, and in greatest measure determine their fundamental differences from the primary lesions.

Due consideration of these facts in relation to the pathogenesis of the secondary lesions known as "*ids*"[1] (or to give them their correct generic name "*microbids*") makes several matters clear.

[1] "Id" or "ide" is derived from the Greek suffix "ides" signifying family class or clan relationship. This use is widespread in almost all branches of science (e.g., in chemistry: oxide, sulfide, lipid, etc.). See Morris Leider, *Aspects of the Allergy of Infection. Quarterly Review of Allergy and Applied Immunol.* 5: 350—379 (Dec.) 1951.

First it is clear that whenever the sensitizing or allergenic properties of the microbic agents are the main factors in the production of the disease, (*e g* in syphilis, tuberculosis, trichophytosis, sporotrichosis leprosy etc.) the "*ids*" will be relatively common while "*ids*" will be practically non-existent in those infections whose manifestations are due mainly to microbic *toxins* (diphtheria, tetanus, etc.)

Second the "*ids*" being essentially allergic manifestations will quite naturally often evidence the well-known cardinal features of allergy Thus certain "*ids*" will tend to resemble one another, even when caused by entirely different allergenic micro-organisms *e g* similar lesions in lichen scrofulosorum and lichen trichophyticus similarities of erythema nodosum due to lymphogranuloma venereum virus and that due to tuberculosis—just as different cases of urticaria or eczematous contact dermatitis will closely resemble one another even when caused by widely divergent *non-microbic* allergens (resemblances between urticarias caused by strawberries, shell-fish or aspirin, etc. similarities between eczematous contact dermatitis due to plants, fur dyes and topical remedies, etc.).

Moreover just as is the case with allergens not derived from micro-organisms, each particular group of microbic allergens will display a certain tendency or preference for producing particular types of characteristic changes. Thus the allergens of the mycobacterium tuberculosis will often produce the secondary lesions of erythema induratum, of papulo-necrotic tuberculids or of lichenoid follicular tuberculids, etc. while allergens coming from epidermophyton fungous infections of the feet will generally produce eczematous eruptions of the hands—(in a fashion analagous to the well-known proclivity of, for example, phenolphthalein and antipyrine to produce fixed eruptions sulfathiazole to produce erythema-nodosum-like lesions bromides and iodides to produce acneform or vegetating lesions etc.).

Still another resemblance between "*ids*" and well recognized allergic reactions to non-microbic products is their common association with a skin hypersensitivity This can be demonstrated through appropriate skin tests with the extracts of the micro-organisms concerned (tuberculin trichophytin, oidiomycin, sporotrichin, histoplasmin, luetin, Frei "vaccine" etc.)

As a rule cutaneous "*ids*" occur only in infections with a demon

strable acquired specific hypersensitivity of the skin—but there are exceptions to this rule—just as there are exceptional instances in which patients with allergic eruptions caused by non microbic allergens fail to respond to skin tests with the clinically implicated allergens. The causes for this lack of response are probably similar in both categories, and include such sources of error as the crude, imperfect and inadequate composition of the skin-test materials the fact that the test materials are applied in a manner by a route and in a concentration differing from that of the actual causal clinical exposure the circumstance that they are applied at a time different from that of the clinical exposure, at sites different from those of the clinical reaction, etc.

In this brief dicussion of the "id" concept I have deliberately omitted any account of the historical developments since DARIER recognized and described the tuberculids (1896) and J JADASSOHN the trichophytids (1911) Nor have I described the clinical and microscopic pictures or many other features of the various kinds of "ids" All these important matters are fully covered in this book by SIMONS, TOLMACH FRANK, and others and my present remarks are intended to serve only as an introduction to the detailed discussions by these other authors.

However in closing, I would like to recapitulate several points, including the following definition of a "*microbid*" which was first submitted in 1940 (*Dermatologic Allergy* p. 207 Charles C. Thomas, Springfield, Ill., 1940).

An "*id*" is a secondary manifestation appearing in a specifically altered (allergic) tissue and produced by micro-organisms emanating from a remote focus, and/or by the allergenic products of such micro-organisms In some instances the tissue-allergy and other local conditions are such that the micro-organisms are rapidly altered, eliminated or destroyed. Under such circumstances the micro-organisms are either demonstrable only with difficulty or are not to be found in the lesions. In classic forms of recognized "*ids*" the distribution of the micro-organisms and/or their products generally takes place via the blood stream but this is not necessarily the only possible route. —While the micro-organisms need not be demonstrable in the lesions of the "*id*" there must be demonstrable previous exposure of the individual to the micro-organism in question (in the form of demon-

strable previous primary lesion(s) or history of primary lesion(s)

"The skins of persons with dermatologic "*ids*" usually have a demonstrable specifically altered capacity to react to extracts of the micro-organism in question, or to reinoculations with the micro-organism. The altered skin reactivity may be hyperergic, hypoergic, or in some instances there may be an allergy of normal type and degree (normergic)"

While it is unlikely that all dermatologists will agree with every detail of the above definition, it may nevertheless be regarded as setting forth the fundamental concepts which have been accepted by most investigators in this field. Surely no one will deny that these concepts of the microbids have proved invaluable for the understanding of many otherwise inexplicable dermatologic phenomena. And, as so often, here too the insight which dermatologists have gained through careful observation of cutaneous phenomena has served to establish general laws and to clarify pathogenetic mechanisms affecting organs other than the skin. For what better working concept is available today than that of the "*Id*" mechanism as a possible explanation of various kinds of arthritis, of certain forms of nephritis and nephrosis, of the numerous mesenchymal, vascular, neural and other forms of damage which clearly *follow a distant focus of infection, but* which *do not* present the characteristic or usual orthodox pathologic picture produced by the micro-organisms concerned in the primary focus, *and which are so often microbically sterile?*

And who today can predict what value the "*Id*" concept may prove to have in future attempts to elucidate the causes and pathogenesis of *a great variety of other important diseases?*

Is it not possible that mechanisms analagous to those producing the known microbids may be at play in such entities as acute, subacute or *discoid lupus erythematosus sclerodermia and sclerodactylia* In various acquired neurologic diseases In sympathetic ophthalmia?

At present it appears distinctly possible that the knowledge gained *through dermatologic studies of the microbids* will some day help to clarify such conditions in which the hypothesis of primarily infectious causes is still fully tenable but in which no known micro-organism or virus *has as yet been proved to be* the responsible causal agent.

# THE "ID CONCEPT"
## (continued)

R. D. G. PH. SIMONS
Amsterdam

DARIER in 1896 was the first to speak of tuberculids by which he meant those cutaneous and subcutaneous processes which, in some unknown way or other were assumed to be related to tuberculosis

These affections, each of which had its own specific morphology were characterized by

(a) their dissemination of appearance, usually symmetrical
(b) their long duration, together with
(c) a tendency to spontaneous recovery [1] and
(d) especially by the fact that they were found to contain no (or in exceptional cases, very few) bacilli

Even inoculation experiments with tuberculid material (bacillus, or filtrable virus?) did not necessarily provoke tuberculosis in the laboratory animal.

The pathogenesis is dominated by three main assumptions, *i.e.*

(1) that toxins are distributed from a primary focus, either haematogenically or lymphogenically (HALLOPEAU BOECK, KLINGMÜLLER)
(2) that a weakened form of the bacillus itself is the cause (JADASSOHN, DARIER) and
(3) that tuberculids are the expression of an existing allergy to the M. tuberculosis (WOLFF EISNER, ZIELER, GOUGEROT) although, on this latter assumption, it is still remarkable that the reaction

[1] But relapses usually occur

(*e g* BAZIN's erythema, granuloma annulare, lichen scrofulosorum and papulo-necrotic tuberculid) differs from any other allergic reaction, no matter what antigen has provoked it, and that, in principle, no "*ens*" ever appears in combination with an *id*"

PAUTRIER considers tuberculids as "*tuberculoses cutanées atypiques*" WOLF and EISNER opined that an "*id*" is a *Lokalreaktion*" when the organism's reactive resistance is raised. That the PIRQUET reaction in tuberculids may turn out negative is attributed by PIRQUET to the fact that the patient's body detoxicates the tuberculin. The antibodies necessary to this end, however appear to be able to act, in support of this hypothesis, without the tissue shock *i.e.* without the allergic reaction.

STOKES states that " the *id*"-eruption is the product of intoxication from the primary focus and not of actual distant dissemination of the infection itself "

MIESCHER, attributes the fact that small foci in particular provoke the occurrence of "*ids*" not to an increase of the allergic reaction or increased immunity but to a lowered immunity The latter may be sufficient as to brake spreading of the original infection, but is unable to prevent local reactions in which also a local process of resistance is present (bacilli negative tuberculoid histology).

SULZBERGER's important vision has been given in the previous chapter

Meanwhile, the "*id*-concept" was despite its imperfectly known pathogenesis a welcome aid as it enabled us better to classify at least provisionally a number of dermatoses for *wo Begriffe fehlen da stellt ein Wort zur rechten Zeit sich ein* ("where understanding fails some word may step in just in time").

The "*id* -concept came into vogue especially in connection with "tropical dermatoses *pianids* in yaws *pintids* in mal del pinto *leprids* [1] in leprosy (the prototype of the *ids*"), and the *leishmanids* in leishmaniasis. We should also mention the *candidids lewurids farids mycids* and *trichophytids* [2]

[1] If it is desired to replace the concept lepra" by "Hansen's disease" in order to do away with the ugly-sounding term, then, if for no other reason, "leprid" should become "Hansenid" (S stoves). At the last Lepra Congress however the ... morbus Hansen" was not adopted or approved of

[2] As to the *syphilids* and *eczematids* these two concepts however differ

The *ids* do not invariably have a specific histological structure. Some have a sarcoid or tuberculoid structure with epithelioid and giant cells; a larger proportion present no specific histological picture whatsoever. In other words, there are sarcoid or tuberculoid and common *ids*"; or better still: *not every id is tuberculoid*.

Histologically many *ids* are indistinguishable from one another. DARIER accordingly says that leprosy, therefore, might provoke tuberculoid lesions of a different clinical aspect, especially some which, so far, have been regarded as tuberculids. According to DARIER, tuberculosis is the most important pathogenic element in the "*ids*" but syphilis and leprosy are also of considerable aetiological importance. We therefore should distinghuish tuberculoid tuberculids, tuberculoid syphilids and tuberculoid leprids. We also know today that malignant tuberous leprosy (classification concept)—now called lepromatous leprosy—is never tuberculoid, despite the fact that benign tuberculoid leprosy (a real "*id*") may sometimes be nodose and even tuberous in its morphological aspect, according to the morphological concept.

Even if—as we argued before—the tuberculin reaction in tuberculids should turn out negative, we should still adhere to the basic principle that a "microbid" must react positively to a test with an "*in*", *e.g.* a tubercul*id* to tubercul*in*, a lepr*id* to lepromi*n* (MITSUDA's test) and a trichophyt*id* to trichophyt*in*, as well as a drug "*id*" should show a positive test to the drug.

The diagnosis gains considerably in reliability when, contrary to expectations, an "*in*" test is followed by a sudden outbreak of more *ids*.

from the others in that (a) syphilids, as a rule, respond to antisyphilitic therapy and disappear when (as shown by Wassermann's reaction) some antigen is still present, and (b) the termination "*id*" in eczematid (a word which, by the way, we [illegible] owe to DARIER) purports to denote that we ha[v]e to do with an affection which, though corresponding histologically to eczema, does not quite correspond to it clinically. DARIER's eczematid is identical with UNNA's seborrhoeic eczema and with BROCQ's seborrhoid.

Names for certai[n] [illegible] [in]toxication phenomena, such as "aurid" for gold intoxication and "*antipyrinid*" for a "fixed" (*i.e.* preferably localized and relapsing [a]t the same place) antipyrin exanthema, belong to the same terminological group as eczematid.

The "ids" are classified as follows in the work of SCHWARTZ, TULIPAN and PECK.

I Epidermal reactions.
- a. eczematoid.
- b lichenoid
- c. parakeratotic.
- d. psoriasiform.

II Cutaneous reactions
- A. diffuse
  - a. scarlatiniform.
  - b erythrodermatic.
- B circumscribed and disseminated.
  - a. follicular (lichenoid)
  - b *non-follicular*
  - c. erysipeloid.

III Subcutaneous reactions

erythema nodosum.
- a. acute benign form.
- b destructive chronic form.

IV Vascular reactions
- a. phlebitis migrans (venous).
- b urticaria (capillary)

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# CLINICAL AND BIOCHEMICAL FEATURES OF THE SKIN IN MALNUTRITION

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During the past three or four decades nutrition research has been concerned largely with vitamins and there has been a tendency to consider malnutrition as being almost always due to deficiency of members of this group of food factors. Indeed for some time investigations were confined to the study of deficiencies of single vitamins in the more florid forms of diseases such as beri beri, rickets and scurvy. It is now however, appreciated that less florid forms of malnutrition are widespread and are usually the result of deficiencies of more than one nutrient. It is becoming clear that in the study of human malnutrition consideration must be given to the composition of the diet as a whole, including its calorie value, protein and mineral content and supply of salt and water.

Malnutrition does not necessarily originate in defects in the diet; it may be secondary to various pathological changes and skin manifestations therefore cannot be considered apart from disturbances elsewhere in the body. Also lesions occur in the integument which resemble those found in malnutrition but which are unrelated to dietary defects. Sometimes skin disease may be due to nutrient failure, for example Darier's disease which is due to a failure of vitamin A (SCHOLTZ and WILLIAMSON).

The *terminology* of cutaneous manifestations of malnutrition is overburdened with names. It has been said (FRAZIER and MARMELZAT) of follicular keratosis that there has been confusion and christening and

rechristening of similar diseases. There are differences of opinion as to the use of the term pellagra which some would restrict to the results of a deficiency of nicotinic acid, while others (GILLMAN and GILLMAN) (SIMONS *et al*) would extend it to include a large group of acute and chronic manifestations of malnutrition, including those occurring in the skin. Further complications have arisen because nutritionists, sometimes with only a rudimentary knowledge of dermatology have described skin lesions, and dermatologists, with little knowledge of nutrition, have written about nutritional defects both are still hampered by a lack of the basic knowledge of the biochemistry and cytology of the skin which is essential to a study of derangements in the tissues.

## BIOCHEMISTRY

The following outline summarises our knowledge of the biochemistry of the skin against which disturbances due to malnutrition should be studied.

Materials concerned in building up the structure and maintaining the functions of the integument are all derived from food. Proteins and minerals are incorporated in structural elements proteins vitamins of the B group and some minerals are known to be involved in intermediate metabolism for which carbohydrates are the main source of energy salts and water are factors in the maintenance of osmotic pressure and the regulation of hydrogen ion concentration. Nutrients are supplied and unwanted products of metabolism are removed by means of numerous small blood and lymph vessels which consist of cells metabolically very active. They depend for their nutrient supply on the fluid flowing through the vessels the fundamental rôle of oxygen in the metabolism of such cells is often overlooked. The functional integrity of the nerve supply of the vessels and tissues in the skin is also of importance and may be affected by malnutrition.

### *Protein*

The skin constitutes an appreciable fraction of the total body weight—about 8 per cent. in the adult. The crude protein content is high about 22 per cent. (MITCHELL *et al*) and in fact accounts for about one-eighth of the total body protein. The turnover rates of skin and muscle proteins measured by isotope techniques are much lower than those of proteins in the blood plasma and viscera, nevertheless together they constitute such a large proportion of the total body protein that 80 per cent. new nitrogen retained in an animal is contained in them (SCHOENHEIMER and RITTENBERG). Protein losses from the skin are normally of the order of 10 g daily In disease as much as 40 per cent. of the daily protein intake may be lost by desquamation (PETERS 1945)

and CUTHBERTSON has estimated the losses after extensive burns to be over 2 kg in ten days. The importance of such losses when related to the protein content of the diet is obvious.

In recent years new physical apparatus and methods, such as electron microscopy (BEAR), X ray spectrography and infra-red spectroscopy (RUDALL) have been employed in addition to isotope techniques in the study of skin and hair proteins and have supplemented studies by cyto- bio- and physico-chemical methods. The results of these investigations, some of which will be briefly mentioned, are leading to a growing appreciation of the intrinsic importance of proteins in skin.



945 Dry finely wrinkled skin of leg of young adult— showing atrophic tissue.

About one half by weight of fat free skin is dense connective tissue this constitutes the corium cutis vera or dermis An important component of this layer is the *ground substance* which is made up of mucopolysaccharide i.e. protein linked either with chondroitin sulphuric acid or hyaluronic acid it 'buffers the supply of water and electrolytes (MEYER and RAPPORT) (ASBOE-HANSEN) The fibrillar elements *reticulin* and *collagen*, are formed in the ground substance by fibroblasts or young fibrocytes Since collagen constitutes 70–80 per cent. of the total skin protein (EISELE and EICHELBERGER) it may well be affected by deficiency of dietary protein. Nothing appears to be known of the origin of the elastic fibres of the corium in inanition they are frayed and fragmented There have been descriptions of degeneration of the elastic fibres in malnutrition (GILLMAN and GILLMAN) (KEYS et al.) and of the collagen fibres in senility (TUNBRIDGE et al.) since elastic as well as collagen fibres are normally involved in the attachments of muscles to the epidermis degeneration may lead to formation of wrinkles and an aged appearance

*Epidermin*, an -fibrous protein of relatively low sulphur content, has been characterised as the main protein of the epidermal cells. It is associated in these cells with a non-fibrous protein of higher sulphur content; the proportions in which these two proteins occur is of the right order to account for the sulphur content of the intact stratum corneum (RUDALL).

The protein of the horny layer of the skin contains *keratins*. In the formation of these, presumably from the epidermal proteins, the *sulphydryl (thiol) –SH groups* are oxidised to disulphide –S–S groups. Cross links are thus provided between clusters of polypeptide chains partially folded or arranged in a spiral thereby



946. Dry staring hair with dyspigmentation (left) contrasted with black, glossy well-pigmented hair. The patient on left had follicular keratosis of the skin of the cheek in front of the pinnae, on the back of the neck and on other parts of the body. Both Chinese boys aged 14 years.

contributing to the strength and chemical inertness of the cornified material (GIROUD and LEBLOND). Kink and curl of hair and the texture of nails, are determined by similar molecular structures.

The importance of the *sulphur-containing amino acids* in maintaining normal nutrition of the skin and appendages has been established in animals (LIGHTBODY and LEWIS) (SMUTS *et al.*). Their rôle in human nutrition is still obscure, as are the effects of other factors on the sulphydryl-disulphide conversion and equilibrium.

Proteins are not only essential to skin structure but are also *enzymes* or parts of enzyme systems. The enzymes in skin include those involved in respi-

ration, in proteolysis in protein synthesis phenolases including tyrosinase hyaluronidase esterases and phosphatases The activity of some of the enzymes has been shown to be most intense in the cells of the inner layers of the epidermis and to lessen in the cells of the outer layers there is a corresponding diminution in sulphydryl groups.

The activity of many enzymes depends on the existence of the -SH groups in their protein moiety The sulphydryl group may be blocked and enzyme activity inhibited Combination of arsenic with the thiol groups of the protein in the pyruvate oxidase of the skin inhibits this system with immediate biochemical effects similar to those found in vitamin-B (thiamin) deficiency (THOMPSON) (PETERS *et al.*) It may not be out of place to draw attention to further similarities between some of the effects on the skin of arsenic and certain manifestations of malnutrition in both there may be altered pigmentation (see Vol. 1 p 183), desquamation sometimes associated with low plasma protein (KEYS *et al.*) and keratosis, of the follicle in subacute and of the skin generally in chronic poisoning

The precise chemical composition of the *melanin pigments* of the skin is not known. As extracted by the usual methods from skin and hair they are part of a complex with protein. There is good evidence that melanin is formed from tyrosine by the enzyme tyrosinase which is a copper protein complex. Several biochemical factors are known to affect melanin formation thiol groups are believed to inhibit tyrosinase action by binding copper (LERNER and FITZPATRICK) Shortage of sulphur-containing amino acids in the diet may reduce inhibitory -SH groups and so modify the redox system in skin and hair that melanin bleaches in sunlight.

In spite of the ubiquity and importance of protein in skin hair and nails and notwithstanding the widespread occurrence of poor protein in human dietaries very little attention has been paid to the relationship between dietary protein and skin nutrition. Evidences of a *protein hunger* have been found in scleroderma, the changes in which have been attributed to the results of a slow type of protein attrition (Co TUI *et al.*) Collagen diseases have recently been investigated the changes in connective tissue found for example in the liver (HILL *et al.*) may be looked for in the skin. For many years malnutrition has been thought to contribute to the formation of bed sores The need for supplying plenty of protein in the diet in the healing of bed sores (MULHOLLAND *et al.*) and surgical wounds (KOSTER and KASMAN) has been recognised (NEEDHAM). This relationship between protein supply and healing of skin lesions deserves consideration in the study of tropical ulcers (see Vol. 1 p 413) which are some of the commonest skin lesions in the tropics.

Confirmation of the existence of protein deficiency is provided by the results of therapy in some forms of malnutrition plasma protein transfusions and protein-rich supplements (especially skimmed milk powder) have been successfully employed in the treatment of pellagra and kwashiorkor

Pioneer research on proteins in skin and hair is being done by those engaged in the study of leather, feathers, wool and fur; the results of such investigations have already helped towards the solution of problems in human dermatology. Dermatologists could profitably pay more attention to work in these technological subjects.



947 West Indian child aged 5 with permanent gooseflesh appearance of skin of neck, folliculosis of face, filiform plugs of chin (dyssebacia). Patient also had depigmentation of the hair, dryness and loss of elasticity of skin of legs, hyperkeratosis of skin of knees and feet, and ulcer scars of skin below the knee.

*B vitamins*

The B group of vitamins includes vitamin B (thiamin or aneurin), riboflavin (formerly vitamin $B_2$), nicotinic acid and its amide (niacin or P-P factor), the pyridoxin group (formerly vitamin $B_6$ or adermin), choline, inositol, pantothenic acid, biotin, folic acid and cyanocobalamin (vitamin $B_{12}$).

It is appropriate for three reasons to consider them here with protein:

1) they often occur in foods which are also good sources of protein well balanced in essential amino acids.

*b*) they frequently function together in biochemical reactions, protein as one part, the B-vitamin in some form as the co-factor (co-enzyme) in an enzyme system, for example riboflavin in flavo-proteins, one of which is concerned in the inactivation of histamine (SWEDIN)

*c*) they are often interdependent with essential amino acids, for example nicotinic acid and tryptophan (CHICK) and methionine and pantothenic acid (LUDOVICI *et al.*).

Most of the knowledge of the rôle of B-vitamins in skin is based on animal experiments the results of which cannot justifiably be transposed to man. However human subjects deprived of *riboflavin* show in the nasal folds on the alae nasi and in the vestibule of nose and ear a fine scaly slightly greasy desquamation on a mildly erythematous base which clears up on administration of riboflavin (SEBRELL and BUTLER).

*Nicotinic acid* is the P-P (pellagra-preventing) vitamin and there is evidence of its value in the disease in humans (CHICK). The aetiology of pellagra however especially the rôle of maize is by no means as simple as this evidence suggests.

By chemical analysis maize appears to contain as much nicotinic acid as many other cereals. However the main protein of maize, zein, contains relatively little tryptophan, an amino acid which is converted in the body into nicotinic acid. A deficiency of pyridoxin and possibly of other B-vitamins interferes with this conversion. There is some evidence that maize contains a toxic factor (WOOLLEY) probably in the outer layers; this substance may interfere with the metabolism of nicotinic acid, *i.e.* behave as an antimetabolite. Even this biochemical basis is too restricted to provide a solution to the problem of pellagra as presented by the GILLMANS.

Skin signs, as well biochemical evidence, of nicotinamide deficiency have been reported in patients on oral treatment with sulpha-drugs and antibiotics: bacteriostatic agents in the gut are believed to suppress synthesis by intestinal organisms which normally produce part of the body's requirements of some vitamins (JOHANSSON and SARLES).

Seborrhoea-like lesions have been induced in man with desoxypyridoxine which is an antimetabolite of *pyridoxin*: they were characterised by exfoliation, redness, desquamation of the superficial epithelium and oiliness, and affected the folds about the nose and angles of the eyes and mouth. They responded to treatment with pyridoxin but not to nicotinamide, thiamin or riboflavin (MUELLER and VILTER).

This observation is of interest in view of the introduction of antimetabolites into chemotherapy, for example the use of certain new antimalarial drugs. It will, therefore, be as well to bear in mind the possible effects of antimetabolites and bacteriostatic agents on the nutrition of the body especially when employing them in the treatment of malnourished patients.

A fine scaly desquamation of the skin and an ashen pallor were produced in human subjects on a diet containing raw egg white (the avidin in which binds *biotin* in the gut) this responded to the administration of a biotin concentrate (SYDENSTRICKER *et al.*)

There have been numerous claims of successful therapy of skin com-



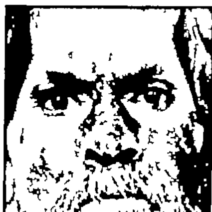
948. Chinese male adult showing seborrhoeic lesions especially of the folds adjoining alae nasi and under the lower lip smooth tongue and angular stomatitis with white appearance of la perleche

plaints with members of the B-complex of vitamins (PLATT 1945) however before these results can be explained or accepted much more research will have to be done into the rôle of these vitamins in skin metabolism and the relationship between their deficiency and skin pathology

*Carbohydrates*

The amount of sugar in the skin varies (URBACH and LENTZ) and is dependent on the diet. Only a small fraction of the carbohydrate is present in the skin as glucose—the rest is in large molecules such as the *polysaccharide* part of the groundsubstance and *glycogen*. The subcutaneous tissues of animals in fact serve as stores of glycogen, the amount found depending on the state of nutrition (SHAPIRO and WERTHEIMER). *Lactic acid* is well-known to

be a product of carbohydrate metabolism it is the main organic acid found in sweat and contributes to the defence of the skin against infection (BERGEIM and CORNBLEET)



949 Pigmentation of exposed part of skin of face known as butterfly patch

*(Gopalan–Coomer)*

Free sugar is the substrate for energy liberating (exergonic) enzyme reactions which are linked with reactions (endergonic) for which energy is needed. Metabolic changes especially the anabolic phases, will be reduced when carbohydrates or other sources of energy are not available this result of malnutrition may be chemically if not cytologically indistinguishable from the effects of shortage of the molecules from which proteins and other complex molecules are built up in anabolism. It will be obvious also that synthesis cannot occur if the catalytic agents —the enzyme systems including their protein and co-factor components—are not available in adequate quantities. Since in normally nourished tissues the various catabolic and anabolic processes proceed in a balanced fashion, relatively excessive demands as in constant loading with carbohydrates, may result in an insufficiency of some factor concerned in metabolism as is known to occur in the case of vitamin B Similar phenomena occur which may be ascribed either to an excess in the diet of a major nutrient or to the deficiency of one of the accessory food factors a common basis for the biochemical explanation is therefore indicated.

It is possible for example, that the oiliness of the skin and seborrhoeic manifestations sometimes attributed to excessive amounts of carbohydrate in the diet and at others to deficiency of a B-vitamin may have the same basis in the inadequacy of some intermediate enzyme reaction. The same end result might conceivably also be due to deficiency of protein for appropriate enzyme formation.

Some recent research (CORNFORTH and LONG) beautifully illustrates the

biochemical basis of a skin reaction the results of a study of the relationship of several hormones, some organic phosphate metabolites dehydroascorbic acid and a sulphydryl-containing substance to the breakdown of glycogen have provided a satisfactory explanation of the alterations of skin sensitivity

*Vitamin C and vitamin P*

The formation and possibly the maintenance of the ground substance of the connective tissue of the skin depends on *vitamin C* supplies being adequate (BALFOUR and PENNEY). In healing wounds it seems as if the formation of reticular and collagenous fibres depends on the accumulation of mucopoly



950 West Indian male of African descent showing dyssebacia. Note filiform plugs of glands, especially on nose and chin.

saccharides. The ground substance and the pericapillary sheath (but *not* the inter-endothelial cement substance) are attacked by hyaluronidase (spreading factor) (CHAMBERS and ZWEIFACH). The attack on the small vessels results in petechial haemorrhages a feature of scurvy capillary permeability is probably unimpaired in ascorbic acid deficiency

Several flavones and coumarins found in plants have the properties of *vitamin P* and are believed to protect the small blood vessels against damage. The precise function of these substances is not known but they are believed to stabilise the ground substance of tissue (LEVITAN). It is therefore of interest that hesperidin, one of the substances with *vitamin P* activity is

when phosphorylated, a powerful inhibitor of hyaluronidase (BEILER and MARTIN).

*Lipids*

About one-eighth of the components of the skin is obtained as an ether soluble fraction (MITCHELL *et al*) it contains fats (glycerides) fatty acids cholesterol phospholipins and wax about one third of this material is unsaponifiable the major portion consisting of sterols. The amount of fatty sub-



951 Dry crackled skin of the legs.

*(Gopalan–Coomer)*

stances l st daily from the skin is from 1–2 g In the surface secretion there are some fatty acids from sweat the epidermal cells contribute a lipid fraction comparatively rich in cholesterol and its esters but the main contribution is from the *sebum* which is present in three approximately equal parts free fatty acids c mbined fatty acids (glycerides waxes and other esters) and an unsaponifiable fraction (ANON 1953). The free fatty acids of the fat of hair contain a fractio n t straight chain saturated acids with odd numbers 7–9 11 or 13 of the carbon atoms in the chain. These acids, which are effectively

fungicidal against *Microsporon audouini* (ROTHMAN *et al.*) occur on adult human hair they are not found in extracts of children's hair

There are few observations on the effects of malnutrition on the skin lipids. Over-feeding undoubtedly affects the amount of skin fat In inanition the layer of subcutaneous fat is further away from the surface and the cells therein are smaller and more widely spaced than in normally nourished people (MCCANCE and BARRETT) The water content of the skin varies inversely to the fat content (WYNN and HALDI) The nature and composition of body fat reflects alterations in the fat and carbohydrate of the dietary



952. "Sooty" lesions of the facial skin.
*(Grzybowski–Warsaw)*

There is confirmed evidence of the need for certain *fatty acids* in the diet of the rat, for example arachidonic, linoleic and linolenic acids which are all unsaturated; if these are not included a dermatitis develops. There is no conclusive evidence that these fatty acids are essential for human nutrition (HANSEN and BURR). In the blood of infants with eczema the iodine value (a measure of the degree of unsaturation of the fatty acids) has been found to be low ([illegible]). Recently low levels of unsaturated plasma fatty acids have been found in Indian children on low fat diets these patients showed poor subcutaneous fat, lustreless, dry and sometimes wrinkled skin, fine branny desquamation and follicular changes—one third of the 48 patients had moderately severe hyperkeratosis There was a good response to treatment with oil of *sesamum indicum* (MENON *et al.*).

*Fat soluble vitamins – A D K and E*

There is no doubt that *vitamin A* is concerned in some way not yet understood in skin metabolism. A direct effect of vitamin A on skin epithelium has recently been demonstrated by FELL and MELLANBY who showed that in the presence of excess vitamin A in organ culture media mucous cells instead of epithelium developed in the tissue.

Much has been written and considerable uncertainty and difference of opinion has arisen over the question of changes in the skin in vitamin A deficiencies In part this is a reflection of the general lack of knowledge concerning cutaneous lesions in any of the deficiency states As WOLBACH points out no one has yet been able to correlate such lesions with known functions of the skin or the normal morphologic sequences of the epidermis and its appendages (YOUMANS)

*Vitamin D* is formed in or on the skin from sterol precursors the part, if any which it plays in skin nutrition is not known. The oxygen uptake of the skin of rats deprived of vitamin D has however been observed to be only 50–70 per cent of that of normal controls and to increase when the rickets heals following the addition of vitamin D to the diet (PRESSNELL).

The chemical compounds having *vitamin K* activity although fat-soluble, are not lipids The naturally occurring substances are derivatives of 1 4-naphthoquinone and are necessary for the formation of prothrombin. If this substance is deficient in the blood clotting may be delayed and haemorrhages into tissues, including the skin, may develop Deficiency may be manifest in the new born infant this is spontaneously remedied when the gut microflora are established. Antibacterial drugs may suppress synthesis in the intestine and produce signs of deficiency which may also follow prolonged failure of absorption of fat as in sprue absence of bile as in obstructive jaundice, and starvation.

*Vitamin E* effects are produced by three derivatives of chromane, the best-known of which is α-tocopherol. Deficient animals show changes in hair and skin no function in man and no effects on human disease has as yet been established

*Mineral elements and water*

The mineral elements found in the skin include iron, zinc, copper manganese, cobalt chlorine, iodine, fluorine phosphorus, sulphur calcium, magnesium, potassium and sodium. By analogy with other tissues some of these may be essential components of enzyme systems, for example *iron* in cytochrome oxidase. It is not surprising therefore to find that the signs of iron deficiency (DARBY 1946) resemble some of those of insufficiency of protein or of certain B vitamins. *Zinc* and *copper* deficiencies affect hair in experimental animals. The rôle of *cobalt* may be clarified as a result of discovering that it is present as an element in vitamin B

In profuse sweating there are heavy losses of *chloride* in chloride starvation as much as 90 per cent of the total chloride lost from the body is from the skin, the blood level remaining constant

*Iodine* an element in thyroxin, has rôle in maintaining normal skin nutrition, and cutaneous manifestations of hypothyroidism are known.

In *fluorosis* skin hair and nails are said to be affected (SPIRA) as well as teeth and bone.

In recent years little attention has been paid to *phosphorus* in nutrition. It is, however, a vitally important element in nucleoproteins and phospholipins. Phosphorus is contained in the substrates of both the phosphorylating enzymes of carbohydrate metabolism and of the phosphatases which are active in the skin, especially during regenerative processes. *Sulphur* is present in the skin primarily in proteins (see p 1480).

*Calcium* enters into the composition of intercellular cement substance: reductions in amount of calcium in these substances are believed to lead to loss of cohesion in the skin (COWAN). LEITHLEIN produced alterations in skin irritability by feeding diets of differing acid and base forming properties and attributed them to changes in the ratio of *potassium* to calcium. The original observation has been confirmed but the explanation is not accepted (VOGT); nevertheless, neuromuscular irritability increases with the concentration of potassium ions. It is of some interest that the ratio of potassium to calcium is nearly four times higher in the epidermis of the normal dog skin than in the corium (EICHELBERGER and ROMA).

In the past decade new views of the electrolyte composition of intra- and extracellular fluids have been introduced; in particular the significance of potassium deficiency has been established (DARROW and PRATT). The relevance of these researches to skin nutrition awaits investigation. The skin and subcutaneous tissues hold considerable amounts of *extracellular fluid* and electrolytes, the chief ion of which is *sodium*. The fluid is not normally free and the space between the cells is not empty but is occupied by a gelatinous matrix, one important component of which is ground substance. In inanition there is an increase in the proportion of the body occupied by the extracellular 'jelly'; many changes may contribute to this increase—these include *a*) lowering of the blood protein, especially albumen; *b*) loss of muscle tissue, fat deposits and protein from connective tissue, and *c*) the effects of endocrine secretions (for example from the adrenal cortex and thyroid) and their behaviour in the body in malnutrition (for example anti-diuretic hormone) (McCANCE). The amount of water in the body is profoundly influenced by nutritional disturbances even if clinical oedema is not demonstrable. The water economy of the skin is also affected in *sweating*; daily losses may vary from about ½ litre in ordinary circumstances to as much as 10 litres or more in hot climates. LADELL has written one of several recent reviews on this subject.

## CLINICAL MANIFESTATIONS

There is no entirely satisfactory *classification* of skin signs of malnutrition. Both MARRACK and LOEWENTHAL have for convenience classified dietary deficiency diseases of the skin as avitaminoses; however LOEWENTHAL clearly stated that alterations in the form of classification might have to be made as research progressed. Preoccupation with avitaminoses has inevitably resulted in little attention being paid to protein malnutrition* which is undoubtedly prevalent among tropical peoples. Furthermore it will be appreciated, from the evidence outlined in this chapter, that cutaneous signs

* I suggest the term 'protein malnutrition' be used for this group of diseases. It would include not only those conditions due solely to protein shortage but also those, such as kwashiorkor and Mehlnährschaden, in which a relative excess of carbohydrate in the diet is an important factor.

of malnutrition may develop from a variety of metabolic and nutritional disturbances. Not only are the clinical and histological manifestations limited in number in relation to the variety of underlying nutritional disturbances but they may not always be pathognomonic of poor nutrition The time has come when continued adherence to rigid classifications can only lead to misunderstanding of the biochemical and cytological basis of the lesions to confusion in interpretation and diagnosis, to disappointment and even disaster in treatment, and to the stultification of research.

Throughout this chapter references are given to papers and monographs containing descriptions of dietary deficiency diseases which show skin signs Brief notes on the signs have been compiled by PLATT (1945) and GOPALAN (1951) In a recent report of an international committee attention has been given to skin signs in the assessment of nutritional status (JOINT FAO/WHO EXPERT COMMITTEE ON NUTRITION).

In chronic malnutrition and partial inanition of some years standing the skin becomes harsh dry rough and lustreless *Xeroderma* was the most common skin lesion encountered in a prisoner-of war camp (SMITH and WOODRUFF) Similar effects have been produced experimentally in adults on a balanced diet of low calorie value (KEYS *et al*) The dryness is associated with impaired function of the sebaceous glands it is conceivable that impaired secretion of sweat may also be a contributory factor and that in dyshidrosis water may not be available for moistening the keratin of the horny layer In long-standing malnutrition the skin, particularly that over the shins may also be thin and *atrophic* the follicles being imperfect or absent, and it may present a shiny or highly-polished appearance. Over pressure areas for example the knees and elbows, the skin may be *thickened* and have a 'velvety' texture The term lichenification is sometimes used, possibly loosely and incorrectly to describe the coarse and grossly thickened skin which is most commonly found over the dorsum of the foot (see Fig 951)

Loose, *finely wrinkled* skin (see Fig 945) is also often seen in malnutrition it is most readily seen by examining the skin of the calves when the subject is kneeling or lying face downward such skin appears to be too large in relation to the volume of the wasted tissues—even if they are oedematous the tissues still may not be able to fill out the skin. If the skin has been stretched by gross oedema the 'bagginess' is accentuated this is seen particularly in the skin of the buttocks when there has been extreme wasting of the gluteal muscles.

*Loss of elasticity* of the skin is evident in inanition. The skin becomes smooth and shiny wrinkles produced by pinching subside slowly and it has a lizard-like or reptilian appearance This condition affords another example (see p. 1478) of the resemblances between some cutaneous manifestations of chronic malnutrition and those of senility

In malnutrition *abnormal keratinisation* occurs in the horny layer and in the

hair follicles and associated sebaceous gland structures. The horny layer may be more or less thickened and may fissure at various levels giving rise to desquamation with small fine flakes large squames or even whole sheets. When newly formed spongy corneum reaches the free surface of the epidermis the squame is outlined and various patterns are produced these have been given names such as crazy pavement mosaic pattern or alligator skin. In chronic malnutrition the skin, particularly that of the legs, may have a



953 Legs of patient with pellagra. Same patient as in Fig 952.

crackled' appearance areas of dry atrophic skin being outlined by fine fissures (see Fig 951 and Vol. 1 – Fig 452)

The follicles may be more or less pouted at the mouth and contain a horny spine of keratin which sometimes encloses a hair *Follicular keratosis* (see Figs. 955 and 956) or keratosis pilaris, occurs most commonly on the extensor surfaces of the arms and thighs when it is severe the buttocks (see Vol. 1 – Fig 172) and parts of the trunk may be affected. The use of the

terms permanent gooseflesh (see Fig 947) and phrynoderma or toadskin has arisen because of the various shapes which the follicles may assume. Follicular keratosis has been attributed to vitamin-A deficiency but it may also develop as a result of deficiency of other food factors Lesions somewhat similar in histological appearance but with follicles containing inspissated sebum instead of keratin, occur on the face and front of the neck. This condition, which has been called *dyssebacia* or sharkskin, has been produced experimentally in riboflavin deficiency in man. (See Fig 950)

Since mild hyperkeratosis pilaris is quite common in otherwise normal children and adults it has been suggested by McCance and Barrett that "these lesions



954 Bitot's spot.

*(Fasal–San Francisco)*

are often an exaggerated response of the skin of certain people to cold, or possibly to the reduced blood supply that accompanies it. It does not seem to matter whether the cold is applied to the surface or produced by a disordered metabolism, but the essential lesion is reduction in the blood supply this is easily understandable Enlarged erector muscles can be demonstrated histologically in the skin of under nourished subjects with follicular lesions (McCance and Barrett)

It is of some interest that patients with signs of protein deficiency complain of the cold even in the tropics (Clark) and that often follicular lesions are

only found in those sites which are subjected to pressure which has presumably produced local ischaemia.

Experiments on human subjects have shown that follicular keratosis may occur on deprivation of ascorbic acid (MEDICAL RESEARCH COUNCIL); the perifollicular capillaries may be engorged or, if not, the application of pressure (SCHEER and KEIL) to the affected limb may produce congestion.

Pallor of the skin has been described as a feature of many malnutritional states, for example in undernutrition, rickets and anaemia. *Skin colour*, so far as it is determined by the vascular supply, depends on both the subpapillary venous plexus and the capillaries; colour changes may be expected



955 Biopsy from arm of patient shown in Fig 957 – note excessive keratosis, remains of keratin plugs at mouth of hair follicles, parakeratosis and abnormal appearance of epidermis. The scar from this biopsy is thin and atrophic (left scar in Fig 957)

as the amount of blood in the vessels is reduced in amount or colour. In malnutrition, dilatation and distortion of the small vessels of the skin have been observed by capillary microscopy and a blanching erythema is an early skin manifestation of pellagra. An erythematous reaction accompanies the seborrhoeic changes in ariboflavinosis. Skin *petechiae* are a feature of scurvy and *haemorrhages* into the skin occur in vitamin K deficiency (see p 1488). Purpura in acute pellagra in young children is followed by the formation of reddish-brown plaques and later enamel spots (see Vol. 1 Fig. 173). In the adult pellagrin, in an acute onset of the disease, the skin is erythematous where it is exposed to light, the parts most commonly

affected are the face and neck, the hands and forearms, and the dorsa of the feet. (See Fig 953 ) SIMONS and SIMONS described linear purpura following scratching and exposure to the sun.

On the skin of the face this erythema may be succeeded by vesicles and on the extremities by vesicles and bullae In pellagra the intensity of *pigmentation* may increase or decrease rapidly over extensive areas of the body the amount and distribution of melanin pigments may be altered, parts of the horny layer may thicken and some skin constituents including the lipids, may oxidise generally to dark-coloured substances Characteristically the pigmentation is symmetrical on the face the 'butterfly' distribution (see Fig 949) is well known and a sooty scaling dermatosis has been described (GILLMAN and GILLMAN) (see Fig 952) Since Old Testament days pigmentation of the skin has been recognised as a feature of famine. Development of a brownish patchy pigmentation was recently observed in human subjects on a low calorie diet (KEYS *et al* )

Dermatoses of the skin of the *external genitalia* are often associated with other signs of malnutrition, for example scrotal dermatitis, which may be mild with branny desquamation or severe with inflammation and itching the skin of the prepuce may also be involved. In the female there may be involvement of the vulva sometimes extending to the labia and adjoining mucous membrane. The tissues of the *mucocutaneous junctions* may be affected, for example the angles of the mouth and eyelids and the anal region. The mucous membrane of the lips may show vertical fissuring (cheilosis) and raw patches with fissuring at the angles of the mouth (angular stomatitis) when infected with *candida albicans* white patches appear this lesion has been known for many years as la perlèche Changes in the lips occur in riboflavin deficiency they sometimes respond to treatment with other B vitamins. The occurrence of la perlèche is not always a sign of malnutrition. Gynaecomastia has been found to occur in association with other evidences of malnutrition. Its appearance is probably due to the effects of malnutrition on the liver which in turn fails to destroy oestrogens.

In various types of malnutrition the *hair* may be dry lustreless, staring and sparse (see Fig 946) in subjects whose hair is normally kinked or curled it may become straight and be of poor quality Loss or alteration of pigment also occurs the earliest change being from black to reddishbrown this change can be reproduced experimentally by oxidising normal pigments and by restriction of sulphydryl-containing substances in the protein in the diet. The time of onset and distribution of dyschromotrichia varies according to the nature and site of the hair the eyelashes differ from the hair of the scalp in that they lose pigment later and more completely and recover more slowly (PILRAERT ) There is no certain evidence that growth of hair is affected in human malnutrition, but it is well-established that growth is impaired in animals fed on diets deficient in the sulphur-containing amino acids cystine and methionine.

The growth of *nails* is somewhat retarded in malnutrition (GILCHRIST and BUXTON) In some nutritional deficiency states, for example shortage of iron, the nails may be thin brittle and altered in shape (koilonychia or spoon nail). In chronic malnutrition the nails are thickened and lustreless.

## DIETARY FACTORS

For good nutrition a diet must supply adequate and properly balanced amounts of nutrients If there is failure to supply enough of one or more food factors then *malnutrition* ensues If there is insufficient food to meet the



956. Section of skin taken during treatment of patient shown in Figs. 955 and 957 Shows stage in return to normal appearance of epidermis, throughout which there are many mitotic figures. Note scar from this biopsy is thick and hyperplastic (keloid).

energy needs of the body then *undernutrition* inanition or starvation develops. In assessing the individual's needs it is necessary to take into account the physical work performed the requirements for growth the special demands of mothers during pregnancy and lactation and, in tropical conditions (MITCHELL and EDMAN) the lowered requirements for energy-rich foods as well as the extra requirements resulting from losses in excessive sweating which however have often been overestimated. The nutritional needs are influenced by pathological changes affecting the gut blood and other organs including the effects of infections and infestations.

It is not always possible to obtain the data on which to assess dietary intake in relation to requirements. The main features of *tropical dietaries* are however known. The average daily intake is about 1800 Calories, little more than half that of people in temperate climates. Three-quarters of the calorie requirement as well as much of the protein and other nutrients are generally derived from a single staple food; this may be a cereal grain, such as maize, rice or sorghum, a starchy root or tuber, for example yam or cassava, or a fruit such as plantain. There is frequently marked seasonal fluctuation in the total amounts of food eaten—calorie intakes per head per



957 Follicular keratosis of extensor surface of arm, before and after treatment with vitamin A.

day may swing from about 2500 or more when food is plentiful to 1600 or less in the 'hungry season'. There is also a seasonal fluctuation in the types of food available and therefore frequently in such nutrients as are derived from protective foods, for example vitamin A (which is almost always supplied as carotenoid precursor) and of ascorbic acid. Apart from seasonal fluctuation, there is a tendency at all times for there to be a shortage of protein, of riboflavin and of other members of the B complex of vitamins.

The protein of tropical dietaries is almost always obtained from primary plant sources; that from rice and lea[illegible]s is of good biological value whilst maize protein is

well-known to be unbalanced with respect to the amino acids needed by man, and some staples, such as the root crops contain very little protein. The deficiencies of protein and B vitamins will be especially pronounced if the staple is of poor nutritive value, for example cassava, and suitable supplementary foods are not available. The amount of fat in the diet rarely exceeds 25 g per head per day and may be as low as 7 or 8 g.

Some deficiency diseases are characteristically associated with the consumption of certain cereal grain products, for example beri beri with highly-milled rice and pellagra with whole maize meal.

In most areas supplies of calcium are low and an intake of 300 mg per day is common. Rickets may develop if this low calcium intake is associated with shortage of vitamin D either because of deficiency in the diet or of failure in the absence of sunshine, to synthesize it from its precursors.

In some districts there is a chronic shortage of iodine.

## CONTRIBUTORY FACTORS

The cutaneous manifestations of malnutrition may be modified by a variety of non-dietary factors. The nature of the skin, and therefore its response to deficiencies, varies in *different parts of the body*. The *age* of the malnourished subject is known to account for clinical differences: for instance in vitamin-A deficiency the follicular changes seen in the adult may not be present in the young in whom the sebaceous glands are not fully developed (FRAZIER *et al*.); some of the clinical features of pellagra are different in children and adults (GILLMAN and GILLMAN). *Environmental factors*, for instance exposure to sunlight (see Vol. 1, Fig. 171) affect the response of the body to chronic malnutrition and contribute to the physical signs of acute deficiency. Constituents of foods and certain metabolites affect skin pigmentation and its occurrence on exposure to solar radiation (see Vol. 1, p. 176). The nature and localization of lesions may depend on *stresses* such as irritation, friction or pressure, as for example in intertrigo and in the follicular keratosis of areas subjected to pressure (see p. 1494). Repeated traumata, such as bites and scratches, which cause damage to exposed parts of the body, may lead to chronic ulceration or if healing occurs to imperfect scar formation. (See Fig. 945.) *Local infection* of lesions may contribute to particular appearances (see Fig. 948) as in the perleche; indeed it would almost seem as if the nature of the soil determines the kind of infecting organisms, and that the latter are in a sense biological indicators of types of malnutrition. *Infections and infestations* contribute in many ways to disturbed nutrition and increased nutritional requirements (DARBY, 1951).

There is growing recognition of the *relationship between disturbances in the skin and those in other tissues and organs*; this is particularly true of the effects of malnutrition. It is often difficult to distinguish between effects directly due to insufficiency of a food factor and those secondary to other disturbances; for example a low protein diet may reduce digestion and absorption in the alimentary canal by affecting the amounts of digestive enzymes pro-

duced, and may thereby add to the direct effects on the skin of shortage of protein Skin disorders may be coincident with the liver damage due to protein deficiency the ability of the liver to synthesise proteins will be depressed and this will add to the effects of the primary deficiency on the skin. The results of liver impairment may be indirect as when oestrogens are not eliminated (DAVIES) but remain in circulation and contribute to modifications of skin responses. Impaired function of the alimentary canal may also affect the contribution of the microbial flora to the supply of nutrients to the body and as in diarrhoea, cause excessive losses of fluids and nutrients Malnutrition sometimes affects secreting glands other than those in the alimentary tract for example the lacrimal cerumenal and meibomian glands. The endocrine glands—pituitary adrenals, thyroid, parathyroid and gonads—may also be affected and contribute to the direct effects of malnutrition on the skin. Nutritional disturbances of the nervous system are sometimes associated with dermatological lesions (SMITSKAMP) when as in beri beri, the cutaneous nerves are involved sensation is affected, sometimes lost. In the so-called dry type of beri beri the skin becomes atrophic. Paraesthesia of the feet, sometimes mild and described as pins and needles sometimes accompanied by intense almost intolerable pain (burning feet) occurs it may be associated with loss of sensation and, according to GOPALAN (1946) responds dramatically to the administration of 40 mg daily of calcium pantothenate.

The fundamental rôle of the blood as a carrier of oxygen has been mentioned (see p 1477) and it not surprising to find cutaneous manifestations in the various *anaemias* The cutaneous changes have been recognised in iron deficiency anaemia (WALDENSTRÖM) (DARBY 1946) in some other anaemias for example that due to deficiency of cyanocobalamin, the effects on the Skin have not been assessed

## DEFICIENCY DISEASE SYNDROMES

In malnutrition cutaneous manifestations are often only one feature of various syndromes. It is manifestly impossible in a limited space to do more than give a few examples. Some of the diseases are well-known, for example beri beri in which, when the disease is uncomplicated, the skin manifestations are comparatively unimportant (PLATT 1951) In vitamin A deficiency *follicular keratosis* may be accompanied by night blindness, xerophthalmia and Bit t s spots (see Fig 954). In ariboflavinosis *seborrhoeic manifestations* occur together with photophobia, lesions of the mucous membrane and tongue, and corneal vascularisation.

A dermatosis may be present in a widespread group of malnutritional disorders known by more than a score of names[1] of which the most popular at the present time seems to be kwashiorkor (BROCK and AUTRET TROWELL

[1] See footnote on page 1489

*et al.*) these occur in young children on diets low in protein and relatively high in carbohydrate. The disease resembles the flour feeding injury (mehlnährschaden) recognised in Europe half a century ago by CZERNY and KELLER. There is some doubt whether even the alteration in hair colour is a constant feature of this disease which can occur without skin changes – the usual accepted features are impaired growth, mental apathy oedema, muscle wasting and the passage of undigested, unabsorbed food.

### THERAPY

The value of treatment with specific nutrients is limited and there have been occasions when specific *vitamin therapy* has been not only ineffective but actually harmful. Successful treatment is in general best achieved by gradually improving the *diet* until it is full and completely balanced.

When there is good reason to believe that a condition is caused by a single predominating vitamin deficiency administration of the deficient factor is justifiable (see Figs 955 956 and 957) doses of 5–10 times the normal daily requirement are generally satisfactory

In severe protein malnutrition it may be necessary to give blood or plasma *transfusions* which should be given slowly and in small amounts blood transfusion is particularly indicated when there is severe anaemia.

Suitable amounts of *protein-rich foods* in particular skimmed milk, can be given by stomach-tube to infants, even if they are seriously ill most young patients however will take a diet rich in protein such as powdered skimmed milk combined with a suitable carbohydrate food (ripe bananas have been recommended (DEAN)) Milk protein in the form of calcium caseinate has been used successfully for infants and young children who did not respond to skimmed milk powder

Unless a good state of protein nutrition has been achieved nutrients which depend for their function on co-enzyme activity may be of no benefit. It is known that riboflavin is not retained in the body when the protein in the diet and liver is low (ANON, 1952) PIERAERTS recognised that certain medicinals for example folic acid, were ineffective until enough protein had been given to clear oedema.

Attention should be given to other aspects of treatment. *Rest* is a valuable and often essential adjunct. Therapeutic *measures against infection* for example of the alimentary tract, and against infestations should be applied cautiously and sometimes delayed until the patient's state of nutrition has been improved. It may even be necessary to reduce the customary dose of some drugs in the treatment of malnourished patients

It goes without saying that the *prevention* of malnutrition in its various forms is by proper feeding the production of sufficient of the right kinds of food however involves consideration of economic and educational problems and other matters beyond the scope of this book.

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## CHAPTER 95

# PORPHYRIA

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### DEFINITION

The term porphyria is used to describe certain related disease syndromes which are associated with a significantly increased excretion (continuous or intermittent) of uroporphyrins and sometimes coproporphyrin in the urine.

The porphyrins are pigments found in many animal and  egetable compounds and very small quantities are normally excreted in human urine. Slightly increased excretion of porphyrins has been noted in certain diseases and intoxications (liver diseases, reticuloses, chemical and heavy metal poisoning, etc.) but markedly increased  xcretion is, with  ery few exceptions, seen only with porphyria.

The excretion of large quantities of porphyrins which occurs in porphyria appears to be the result of  metabolic defect, and it has been suggested that this defect is inherited as  mendelian recessi  in  congenital" porphyria and as a mendelian dominant characteristic in "acute" and  chronic" porphyria.

An associated sign in many cases of porphyria is a tendency to certain skin changes, particularly bullous eruptions of exposed parts, but the exact relationship of the cutaneous lesions to the metabolic defect is uncertain. It is possible that no causal relationship exists between them, but that the two are genetically linked.

I  me type  f porphyria  bdominal and nervous symptoms predominate over any cutaneous manifestations, or skin lesions may be entirely absent. It has also recently been discovered that many patients with porphyria of  ll types have  haracteristic lesions of the ocular fundus. (These findings will shortly be published by B [illegible] rs and Bos [illegible] of Johannesburg.)

The porphyrias are classified into two main groups

(A) Porphyria with marked cutaneous lesions and

(B) Acute porphyria in which abdominal and nervous symptoms predominate.

Group (A) can be split into *congenital porphyria* (where signs of disease are evident from birth or appear shortly afterwards) and *chronic* or *delayed cutaneous porphyria* (where signs of disease only appear much later in life) and group (B) can also be subdivided according to the predominating symptoms

As more and more cases of porphyria are discovered it is becoming



958 Chronic porphyria showing ruptured bullae, hyperpigmentation, hypertrichosis and blepharochalasis.

*(Borbeff-Jelmesberg)*

increasingly obvious that this clinical classification is only of superficial value *Formes de passage* are being found, especially between the acute and chronic varieties, and it is possible that, in time, the members in the group of porphyrias may be shown to be different manifestations of a single entity

The porphin nucleus, the basis of the porphyrin compounds, is composed of four pyrrole rings linked at the alpha positions into a larger ring by means of four =CH— bridges There are eight replaceable H atoms in this nucleus at the beta-

positions of the pyrrole rings, and the properties of the individual porphyrin compounds depend on the presence of various substitution groups in these positions. Details of the chemistry and identification of the porphyrins can be found in articles by BARNES and MARSHALL and by WATSON. The porphyrias cannot, however be classified according to the types of porphyrins excreted.

Although porphyria may be suspected in certain cases not exhibiting porphyrinuria, *a positive diagnosis can only be made by the discovery of an excess of porphyrins in the urine* The presence of porphyrins may be suspected because of colour changes the urine may be brownish, pink or red. Rapid exact identification is best made by direct spectroscopic examination the quantities of porphyrins present in normal urine are not thus detectable, so that if the characteristic bands are seen it is certain that the urine, whether visibly discoloured or not, contains an excess of porphyrins. It must be noted, however that *patients with porphyria do not at all times have porphyrinuria* the quantity excreted varies greatly and *a single negative test in a suspect case does not exclude the diagnosis of porphyria*

Although it is probable that a liability to the metabolic, and probably the cutaneous, defects is present at all times in all cases of porphyria, signs of disease only become evident, in the majority of cases (*i.e.* acute and chronic types), later in life, oftenest in the third or fourth decades. Alcoholism has been suggested as a precipitating factor in chronic porphyria by BRUNSTING and MASON and the possibility of nutritional deficiency and alcoholism affecting liver function and producing increased porphyrin excretion is discussed by RIMINGTON and LEITNER. VILANOVA *et al* have suspected hepatitis, syphilitic or otherwise. All these possible factors could be implicated in South Africa where a great many cases of acute and chronic porphyria have been discovered in recent years (BARNES, 1945 1951 BARNES and MARSHALL).

It was once believed that there were two (clinically indistinguishable) forms of acute porphyria, idiopathic and toxic. Drugs such as sulphonal, trional and the barbiturates were thought to cause the toxic variety It now seems likely that this distinction is artificial and that *the so-called toxic type was diagnosed in patients treated with sedatives for psychotic manifestations of unrecognized porphyria.*

## EPIDEMIOLOGY

Sweden is the only country apart from South Africa in which relatively large numbers of cases of porphyria have been discovered (WALDENSTROM WALDENSTROM and VAHLQUIST) It cannot yet be decided whether this odd distribution of a disease group generally described as rare is significant, or whether it is due to "porphyria consciousness" in those countries

The cases seen in South Africa do not differ significantly from those discovered in other parts of the world In describing the porphyrias the different types will be considered against a background of the cutaneous features

## SYMPTOMATOLOGY

The cutaneous lesions here described may be found in greater or lesser degree in all the varieties of porphyria. There are three common signs *a bullous eruption on exposed parts hyperpigmentation* and *facial hypertrichosis* any one or all of which may be seen at a given time.

*The bullous eruption* most commonly affecting the hands, feet and face, resembles simple or dystrophic epidermolysis bullosa or hydroa aestivale. Some patients have recurrent attacks (usually lasting a few months) others are continuously affected. The stimulus producing the lesions may be traumatic or actinic or both. It is sometimes difficult to determine which stimulus is implicated in a given case, and the effectiveness of these stimuli may alter in the course of the disease. Such bullous eruptions are commonly seen in Bantu patients in South Africa and it is interesting that natural pigmentation affords no protection against the sunlight in sensitive patients.

The size of the bullous lesions varies greatly and the skin involved is not always only that exposed to light. Bullae may be found at any friction point. In one case of chronic porphyria enormous bullae formed all over the trunk and might have been mistaken for lesions of pemphigus vulgaris Bullae contain clear or bloodstained fluid and their roofs are usually quickly ruptured leaving clean raw erosions which heal if not secondarily infected, in one or two weeks. Some lesions heal completely and leave no trace, but most patients who are

so affected show some oval or circular scars which may be hyper or de-pigmented and the appearance and distribution of these scars may suggest the diagnosis even during latent phases. Small epidermal cysts milia, may be found in the scars. The skin in the affected areas may become atrophic, and the nails may be loosened and deformed by subungual bullae. Scarring and atrophy seldom lead to gross deformity or mutilation except in the congenital variety

*Other eruptions* The skin lesions are not always bullous sometimes there is no history of bulla formation and yet the patient can present scars on exposed parts indistinguishable from those left by a bullous eruption In such cases the skin is either fragile and easily scraped off by minor injuries, or there is an increased liability to minor infections, again without bulla formation.

*Pellagriform dermatitis* has been noted in some Bantu patients in association with bullous eruptions or scarring, and VILANOVA *et al.* have described vesiculo-oedematous dermatitis of exposed parts. It is not certain that pellagriform dermatitis is a manifestation of porphyria pellagra is common in the Bantu and the two diseases can co-exist in one patient. But there is no evidence, in spite of statements to the contrary that pellagra and porphyrinuria are directly associated. In a number of Bantu patients with chronic porphyria I have noted a striking velvety warty hyperkeratosis (not sufficient to deserve the name of knuckle-pads) over the two terminal knuckles of all the fingers. Histological examination in two cases showed a pure hyper keratosis the stratum corneum being about three times the normal thickness.

*Sclerodermatous changes* in the skin, as described by TURNER and OBERMAYER, have not yet been seen in any South African case.

*Hyperpigmentation* of the exposed skin, of the cheeks and temples particularly is commonly seen and is especially marked in the Bantu where the colour change varies from deep chocolate brown to jet black. In some cases the whole body surface may be hyperpigmented.

This colour change may be the only cutaneous sign of porphyria and has been the only reason for bringing patients to hospital in several

cases. It can closely resemble the hyperpigmentation of pellagra, and it should be a rule to examine the urine of any atypical case of pellagra for porphyrins.

*Hypertrichosis* of the face is quite often seen in women especially Bantu. It is more difficult to determine in men but has been found in a few South African cases. The areas affected are those between the outer ends of the eyebrows and the temples, and the cheeks one or both areas may be affected in a particular case. More rarely there is hypertrichosis of the arms and legs. In a very few women a heavy growth of hair on the upper lip has been noted. Hypertrichosis as a solitary cutaneous sign of porphyria has not been seen in South Africa it usually accompanies hyperpigmentation.

## CONGENITAL PORPHYRIA

This is the rarest form of porphyria and TURNER and OBERMAYER could find descriptions of only 86 cases (not all of them entirely convincing) in the literature before 1936 few have been added since. The metabolic defect is established in pre or early postnatal life and signs of disease are present at birth or appear soon afterwards Congenital porphyria is characterized by the passage of discoloured urine containing large quantities of uroporphyrin 1 and small quantities of coproporphyrin, cutaneous photosensitivity staining of teeth and bones and sometimes, in the later stages, splenomegaly and haemolytic anaemia.

The first South African case, a good example of this type, was recently reported by FINDLAY and BARNES. The patient was a Bantu girl of 13 years, and signs of disease (red urine skin lesions and hypertrichosis) had appeared when she was 11 months old Skin lesions continued to appear thereafter on exposed parts at all times of the year and seemed to be unrelated to trauma and the urine showed varying shades of red. While under observation bullae were seen on the skin and there were pigmented and varioliform scars on exposed parts. The exposed skin was hyperpigmented, dry and inelastic. The fingers were claw-like and their movement was restricted. There was hypertrichosis on the face, arms and legs The permanent teeth showed brown staining of the crowns and fluoresced rose pink under Wood light. The milk teeth were said to have been red or pink in colour The e was no abnormality of the endocrine or nervous systems and the child was intelligent The spleen was slightly enlarged liver function tests, liver histology (biopsy) and electrophoretic fractionation of the serum proteins were abnormal.

Reports indicate that intercurrent pulmonary tuberculosis is a common cause of death and that death is seldom directly related to the metabolic defect.

## CHRONIC PORPHYRIA

Chronic, or delayed cutaneous, porphyria is often seen in South Africa where it is commoner in the Bantu than in the European. Cases have also been seen in coloured (Afro-European) people.

The signs of disease are mainly cutaneous and have the characteris-



959 Chronic porphyria showing pigmented and depigmented scars, hyperkeratosis of the knuckles and nail dystrophy

*(Kerr—Johannesburg)*

tics already described. The skin lesions vary greatly in degree and severity from case to case, but they are generally less marked than in congenital porphyria. Mutilating or disfiguring scars are rarely seen in chronic porphyria, but we have seen one or two cases so affected. The urine may be obviously discoloured, but sometimes porphyrins (of a type still under investigation) can be detected spectroscopically in apparently normal urine. The first signs of disease usually appear during the third or fourth decade, but children have been affected.

In pure chronic porphyria there are no abdominal or nervous signs or symptoms. The diagnosis of typical chronic porphyria pre-

sents no difficulties if the observer is aware of its existence. *Formes frustes* with no bullous lesions or with only facial hyperpigmentation can very easily be missed. Patients seldom refer to colour changes in the urine unless specifically asked, and such changes are often slight. The diagnosis can generally be confirmed during an active phase by finding porphyrins in the urine but it must be remembered that the *quantity* excreted fluctuates and may, at times, be normal. This is an important point: it is my belief that a diagnosis of non-porphyrinuric epidermolysis bullosa or hydroa aestivale should only be made in cases where the urine has been regularly examined, and found free of excess porphyrins, over an extended period.

The prognosis as regards survival is good in pure chronic porphyria.

## ACUTE PORPHYRIA

Acute porphyria is a chronic disease with acute episodes. Most of the South African patients have been Europeans, but a few Bantu and coloured people have been affected (WOODS and BARNES). The condition is commoner in women than in men and the age at onset is generally in the thirties or forties. The prognosis is not good: the patient may die in the first attack, recover and live for many years without another attack, or have occasional or frequent recurrences.

The clinical picture in an acute attack varies greatly from case to case, and sometimes from attack to attack in the same patient. Symptoms include acute abdominal or neuritic pain, constipation, vomiting, muscular wastings, weakness or paralysis, and very variable psychotic manifestations. Death is often due to respiratory failure following an ascending paralysis. The urine during attacks contains porphyrins (type still under investigation) and porphobilinogen. This latter substance is colourless, but if the urine is left standing it is converted, in an hour or two, to dark red porphobilin. Porphobilinogen, which is excreted only by patients with acute porphyria, can be identified in fresh urine by WATSON and SCHWARTZ's test. More detailed studies of the abdominal and nervous manifestations of acute porphyria can be found in articles by NESBITT, BARNES and MARSHALL, and WOODS and BARNES.

It is generally stated that cutaneous lesions are rare or slight in acute porphyria. They may be insignificant in comparison with the other

signs and symptoms but their rarity is, in my opinion, exaggerated. In many descriptions of cases of acute porphyria in the literature there is no mention of the state of the skin and we may conclude that it was not specifically examined.

The skin lesions in patients with acute porphyria are of the varieties already described, but they are generally of milder degree than those seen in the other two types of porphyria. During an acute attack it is unusual to find active bullous lesions but scars of earlier lesions can often be found, although they are sometimes only slight. There are certainly some cases of acute porphyria where no cutaneous lesions ever occur



960 Blisters on the middle toe Scars and dystrophy of the nails.
*(Barnes–Johannesburg)*

*The diagnosis of acute porphyria is seldom easy and patients with abdominal symptoms are liable to be subjected to unnecessary abdominal operations One patient recently seen had had eleven major operations she also suffered from a recurrent vesicular eruption on the nose In cases of abdominal pain of obscure origin it should be a rule to inspect the skin examine the urine for porphyrins and view the ocular fundus as well as checking pupil reactions to exclude tabes dorsalis*

## TRANSITIONAL AND ATYPICAL FORMS

Many cases of porphyria seen in South Africa have exhibited signs and symptoms of both chronic and acute porphyria and in some cases precise classification into one or other group is impossible.

Patients with pure chronic porphyria present no evidence of abdominal or nervous disease but one may often obtain a history of chronic constipation, and several patients have complained of paraesthesiae or muscular cramps but had no demonstrable abnormality of the nervous system.

In a few cases of chronic porphyria patients have complained of attacks of abdominal cramp during phases of cutaneous activity but in the absence of any other evidence of acute porphyria they could hardly be so classified. In two cases of active chronic porphyria I have seen the patients develop obvious psychoses again without any other sign of acute porphyria. Classical acute porphyria can, of course, supervene in a case of chronic porphyria.

The picture in congenital porphyria is more precise, but there are cases of cutaneous porphyria occurring in children which are very difficult to classify Identification of the type in such cases depends on the history to some extent on the presence or absence of staining of the teeth, and on the type of porphyrin excreted

Completely *asymptomatic porphyria* where the only abnormality is porphyrinuria, is sometimes discovered in relatives of patients with overt porphyria.

## OCULAR LESIONS

Lesions of the external structures of the eye, analogous to the cutaneous lesions, have frequently been described in cases of porphyria, but examination of the fundus has until recently received little attention The recognition of the lesions of the fundus which can be discovered in a significant proportion of cases, may prove to be of diagnostic importance in certain cases where positive evidence of porphyria is otherwise lacking I am indebted to BARNES and BOSHOFF for permission to quote from an article on "Ocular lesions in patients suffering from porphyria" in which 67 cases are studied.

*Ocular Adnexa* Bullous lesions oedema, scarring and pigmentation may occur on the lids and can result in deformity and ectropion Loss of elasticity of the lids is common and there may be equal or unequal blepharochalasis. The lids were affected in 19 of 67 cases

*Conjunctiva* The conjunctiva was affected in 12 cases There may be congestion in the absence of any adjacent skin lesions. Bullae may result in varying degrees

of symblepharon. Scars may form on the palpebral conjunctiva, usually under the lower lids, and generally resemble the "en plaque" type of trachoma scar. Marked thickening of the interpalpebral conjunctiva is often seen.

*Sclera*. The commonest lesion, referred to as scleromalacia perforans, is seen in congenital and chronic porphyria but BORHOFF notes differences between this and true scleromalacia perforans.

*Cornea*. The cornea may be affected by a keratomalacic type of lesion, *e.g.* perforation, scarring and leucoma adherens. The affection is usually severe, scars are dense and blindness can result.

*Iris and Lens*. The iris may participate in leucoma adherens.

*Fundus*. The fundus is rarely mentioned in studies of porphyria and the only detailed study is that of JAFFE who described one case showing retinal haemorrhages. BARNES and BORHOFF record fundus lesions in 34 cases.



961 Fundus lesions. Above the disc is an "en plaque" type of lesion with pseudopodia. Other lesions present are pigmented globules and patches and depigmented patches, annular lesions and macular pigment shift.

1. Those lesions mostly seen during acute cerebral episodes of acute porphyria are situated mainly in the retina and are oedematous in their early stages. There are two varieties, (a) round patches of oedema with a cotton-wool appearance, and (b) flat thin oedematous films occurring mainly at the periphery. In all cases of type (b) there is general choroidal paleness and a slightly swollen hazy disc. Healing leaves varying degrees of pigmentation.

2. Scarring is the commonest lesion seen in congenital and chronic porphyria. There are again two types: (1) the slowly progressive discrete annular type, with zoned areas of varying pigmentation, and (2) diffuse, rather dense choroidal lesions in plaques of clover-leaf shape, extending from the disc and covering the macula. There may be serious impairment of the vision with type (1) and complete permanent blindness with type (2).

3. A third group of miscellaneous lesions of uncertain significance is also detailed.

## THERAPY

No specific treatment for any form of porphyria has yet been discovered. The traumatic and actinic cutaneous lesions of chronic porphyria usually heal while the patient is in hospital under investigation only to recur on his discharge. A measure of protection is given to light sensitive patients by the use of a barrier substance such as 15 % *para*-aminobenzoic acid in vanishing cream and avoidance of exposure to sunlight, when practicable, serves to minimize the formation of new lesions Mepacrine (100 mg thrice daily less when the skin becomes stained) *may give spectacular relief*

In acute porphyria dehydration must be relieved and sedatives particularly barbiturates, should not be used.

Injections of crude liver extract, kaolin by mouth (Abrahams *et al.*) vitamins and a variety of other remedies have been suggested and tried in the porphyrias but none appeared to have any beneficial effect in the South African cases

Many South African Bantu patients had serological evidence of syphilis (repeated tests) A number of such cases with chronic porphyria were treated with penicillin, but the cutaneous lesions were not influenced. It is conceivable that porphyria may be a cause of biological false positive reactions but this possibility has not yet been investigated.

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# TUMOURS

## CHAPTER 96

# BENIGN TUMOURS OF THE SKIN

EUGENE F TRAUB – New York

DANIEL SCHULTHEIS Jr – New York

### I. CONNECTIVE OR FAT TISSUE ORIGIN

*Fibromata* are benign tumours composed of fibrous connective tissue cells and fibers which develop in the cutaneous or subcutaneous tissue. They can be single or multiple flat, sessile or pedunculated hard or soft congenital or acquired – in some multiple lesions, there may be pigmentation.

#### FIBROMA MOLLE

*Fibroma molle* is soft, pin head to child s head in size and of a flabby consistency It may be yellow reddish-blue, or normal skin colour. Face trunk and female genitalia are most common sites. Digital compression causes some of these tumours to disappear through a ring in the skin.

*Histology* Fibroma molle is composed of connective tissue fibroblasts and a collagenous intercellular fibrillar substance which is a product of the fibroblast. (KYRLE) There is an irregular swirling pattern of the cells and fibrils. There is usually band of normal connective tissue separating the tumour from the epidermis. Blood vessels are seen mostly at the base while sebaceous glands and hair follicles are usually lacking and there is little or no elastic tissue in the growth.

#### FIBROMA DURUM

*Fibroma durum* – dermatofibroma lenticular (SCHREUS) Noduli cutanei (ARNING and LEWANDOWSKY) is firm to hard, sharply defined, usually covered with normal skin unless trauma has caused secondary changes.

The size varies – small pea to walnut, usually with a broad base, though sometimes pedunculated and it is found usually on the legs or arms There is little tendency to regression, a lesion attains its size and remains stationary

*Histology* Fibroma durum results usually because of a productive inflammation with fibrosis the epidermis usually atrophies though it may be acanthotic. There is a circumscribed though not encapsulated connective tissue proliferation of the corium. Connective tissue bundles lose their form and arrangement and individual strands are much thickened and may appear homogeneous. A band of normal connective tissue separates the growth from the epidermis Cutaneous appendages are absent in the lesion proper Fibroma durum is practically avascular with no nerve tissue elements and little or no elastic tissue.



962. Keloid following piercing of the earlobe

*Treatment*

1. Fibroma molle – surgical excision of the larger lesions while electro-desiccation may be performed on small ones.
2. Fibroma durum – no need except for cosmetic purposes – surgical excision or radiation.

**KELOID**

This tumour consisting of connective tissue, usually follows trauma in predisposed persons though trauma is not always necessary

Types

(a) True – spontaneous idiopathic

(*b*) False – spurious, cicatricial (develops in a scar or following trauma [1])

While keloids are most frequently found on the anterior chest (sternum) they may occur almost anywhere. MOOK described a case on the tongue. *Involution and complete disappearance is rare.*

They consist of whitish or reddish globular or semi-globular nodules or plaques which are usually slow of evolution. They have a roundish or ovoid outline and linear elevated striae, bands, ridges, ribbons or tapes in irregular outline and disposition are the rule usually

The tumours are observed in all ages and in both sexes. The Negro is particularly predisposed to keloid formation and to larger keloids than other races. They are either black or devoid of pigment in the Negro.

Subjective symptoms are rarely noted, except for pruritus in the early stages and mild stabbing pain in older lesions. The surface is smooth and hairless and frequently shows telangiectasia.

*Histology* Keloid, like the dermatofibroma is a form of hard fibroma, consisting of a dense and sharply defined connective tissue growth, limited to the corium. *Large numbers of connective tissue cells are seen early but later become much* less frequent. The cells have long oval bodies with large vesicular nuclei showing numerous regular mitotic figures. The bundles consist of coarse collagenous fibers which run parallel to the skin surface, but which intertwine and cross with neighbouring bundles.

*The true or spontaneous keloid* ways originates in the corium proper and later in growing, the papillary bodies and rete pegs become altered or destroyed and there is pressure atrophy of the epidermis.

*The false or hypertrophic scarring keloid* shows alterations from the beginning in the papillary bodies. The elastic tissue is almost completely absent in the tumour mass. The final fibrotic tumour mass may become encapsulated by surrounding normal connecti tissue. The skin appendages are pushed aside by the tumour and become atrophied.

Extending from the growth are masses of cells usually *surrounding the blood* vessels and it is due to these cells that recurrences occur after the supposed extirpation of the mass.

*Treatment* Treat as early as possible with radiation. Old lesions should be excised and the area may be treated with radiation or cortisone may

[1] A hypertrophic scar does not exceed the outlines of the previous scar as keloid always does.

be injected directly into the site. Solid carbon dioxide applied with moderate pressure is often successful.

## MYXOMA

This is a benign tumour of the skin consisting of myxomatous tissue. It may vary greatly in size and is usually soft, pink to red in colour. It has been observed in the cutaneous and subcutaneous tissue of the cheeks, axillae, genitalia, back and thighs. On cross-section it appears transparent and a clear jelly-like fluid can be removed. A true myxoma is rarely seen. It may be present at birth and therefore is considered to be "anlage" in the embryo.





963 – 964 Xanthomata tuberosa.
*(Siemens–Leyden)*

*Histology.* The tissue is similar to WHARTON's jelly of the umbilical cord. It is found nowhere else in the human body. Loosely arranged spindle-shaped connective tissue cells with long branching processes are seen while homogeneous mucin may be noted between the cells. Blood vessels are abundant and surrounded by lymphocytes and leukocytes.

*Treatment.* Electro-cautery or surgical excision. Recurrences are rare after removal.

## XANTHOMATA

*Xanthomata* are tumours of lipoid histiocytes and fibrous elements and were first described by RAYER. They are circumscribed yellow to reddish-yellow formations ranging from millet seed to walnut in size and may at times coalesce. The surface may be smooth, rough or uneven – localized or disseminated. Usually seen over elbows, knees and hips though they have been frequently observed on the palmar and plantar surfaces as well as on the eye-lids and on the trunk. Over the joints, the lesions are grouped. At times the mucous membranes are involved. Xanthomatous infiltration of the lines of the hands may



965 Reticulo-granuloma eosinophilicum Cutis simplex. Giant cells, foam cells, eosinophils and histiocytes.
(*Verdonck—Univ. Amsterdam Dept. Dermat.*)

occur without tumours in both diabetics and non-diabetics. They are found usually in middle age. Spontaneous involution is rare.

*a* *Xanthoma palpebrarum or xanthelasma* are found only on the eye lids, are flat yellowish-gray elevations of which 70 % may show elevation of blood lipoids (cholesterol). HOPKINS reported a high incidence in lepers, with associated hyperlipaemia. Cardiovascular changes may be predicted.

*b* *Juvenile xanthomata* are smaller, more irregularly arranged and

more red in colour with a tendency to spontaneous involution. Usually occur as *Xanthoma tuberosum* They are sometimes seen in association with HAND-SCHÜLLER-CHRISTIAN disease.[1] Some authors refer to these as *Naevoxanthoendotheliomata*

*c* *Xanthomata diabeticorum* are usually multiple, appear suddenly as small yellow to brown discrete papules nodules and confluent plaques most on the extensor surfaces, with predilection for palms and soles the eye lids are usually free. This type of lesion often has an inflammatory base which gives it a reddish or violet colour Unlike the other xanthomata, this type is usually accompanied by pruritis, burning and tenderness and is usually associated with rather severe diabetes where hyperlipemia is marked. In many cases they undergo involution under dietary regime and insulin therapy

*d* *Xanthomata tuberosa* are most common next to xanthelasmata and begin at any age. Papules nodules tumours, infiltrated plaques striae or non-elevated smooth plain areas predominating on the extensor surfaces They are yellow or yellowish red, usually grouped about large joints but may occur over the small joints of hands palmar and plantar surfaces. Tendon sheaths may be involved In children, the eruption begins shortly after birth. (Complete involution usually does not occur) They may develop at sites of trauma. In practically all cases there is an increase of cholesterol and total lipoids in the blood serum. Cardiovascular symptoms (angina pectoris) are usually seen especially in females 50 years old and upward.

*e* *Xanthomata disseminata* consist of fine papules and plaques pre

[1] HAND-SCHÜLLER-CHRISTIAN's disease implies a syndrome consisting of diabetes insipidus, exophthalmos multiple defects of the bones, and occasionally xanthoma disseminatum-like lesions of the skin Probably this disease, together with LETTERER SIWE's disease and eosinophilic granuloma of bone, represents a group within the histiocytoses The former reveals petechiae, papules, and pustules in the presence of fever, anaemia, hepatomegaly and splenomegaly and is almost always fatal It occurs usually in infancy Eosinophilic granuloma is a bone-disease which may be accompanied by brown macular and ulcerative lesions of the skin and seborrhoea-like lesions on the scalp (WOERDEMAN and PRAKKEN). According to these authors the eosinophilic granulomas of the skin should be classified as follows granuloma eosinophilicum diutinum faciei, reticulo-granuloma eosinophilicum cutis (termed — simplex when only localized in the skin), granuloma eosinophilicum pemphigoides and granulomata eosinophilica cutis are for the heterogeneous group of eosinophilic granulomas, which cannot be classified among the former ones

dominating on the flexor surfaces, especially in the axillae, face and mucous membranes. Xanthelasma is usually seen in association with this. Blood lipoid levels are normal or even subnormal and there is a definite cholesterol elevation, especially cholesterol esters. Cardiovascular changes are not found. These cases are relatively uncommon and in none of the patients has there been evidence of HAND-SCHÜLLER CHRISTIAN disease.

*Histology* The nodules are composed of foam or xanthoma cells together with Touton giant cells. (Nuclei completely surround deposits of lipoid in the cytoplasm.) Polariscopic examination reveals double refractile cholesterol crystals. In the early stages there is an inflammatory reaction. Even the endothelial cells of the walls of the small capillaries participate in forming xanthoma cells. The xanthoma cells are considered to be histiocytes containing lipoid rather than a true tumour cell

The picture is the same in xanthelasma except that relatively few Touton giant cells are seen.

*Treatment*

| | |
|---|---|
| 1 low fat diet (animal fat free)<br>2 lipocaic (pancreatic hormone)<br>3 surgical intervention | xanthoma tuberosum |
| 1 surgical excision<br>2 electrolysis<br>3 CO snow<br>4 trichloracetic acid | xanthelasma |
| 1 dietary regulation – plus insulin | xanthoma diabeticorum |

Xanthoma disseminatum show no response to treatment but usually progress with terminal involvement of the liver and death from inanition or intercurrent infection.

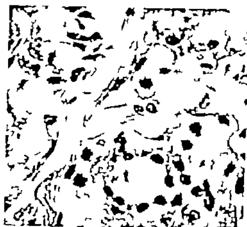
*J Extracellular cholesterosis* (URBACH) are lentil-sized, hard translucent nodules or vesicles of extracellularly-deposited cholesterol. They are yellow initially later becoming violet or reddish-brown. The lesions are located on the skin and mucous membranes and show a tendency to coalesce. They are found on the chest, upper arm (extensor surface), buttocks and hands. The lesions usually occur in crops and may be verrucous. The spleen is hard and enlarged. No hypercholesterolaemia is found but a disturbed hepatic function and lipoid metabolism are to be expected.

*Histology* Severe damage to vascular endothelium in the cutis, infiltration of round and spindle cells with haemorrhage and cellular disintegration. The lipoids are extracellular with large amounts around vessels, spreading to involve the entire cutis. No foam cells found.

*Treatment*

1 Repeated radiation.
2. Low diet in fat.

*g Lipoid proteinosis* (Lipoidosis cutis et mucosa) URBACH – generally begins in infancy involving the mucous membranes of lips, mouth



966 Xanthoma with Touton giant cell.

and larynx, later followed by cutaneous manifestations Hard yellowish infiltration on inner surface of the lips soft palate uvula and under surface of the tongue (tongue may have a hard wooden consistency). A child is unable to talk. Tracheotomy may be necessary because of stenosis of the larynx. On the face, yellowish nodules can be seen together with variola-like scars. A secondary variety of the skin manifestations consists of hyperkeratotic lesions on dorsa of fingers, elbows and knees There is a definite hereditary tendency and a family history toward diabetes. Blood lipids are essentially normal – or there may be an increase in lecithin.

*Histology* Extracellular deposits of lipoids forming a mantle about blood vessels and also forming homogeneous diffuse infiltration of the connective tissue, hence merging of the lipoid and protein. No foam or xanthoma cells and no necrosis.

*Treatment*

1 None satisfactory
2. Insulin – (TRIPP)

**LIPOMAS**

*Lipomas* are lobular tumours composed of fat tissue and surrounded by a fibrous capsule located in the corium and subcutaneous tissue



967 Lipoma: Group of fat cells which are held together by a capillary network forming lobules which again are united by connective tissue trabeculae.

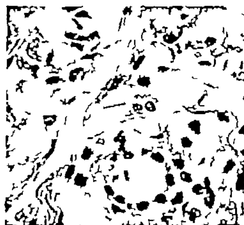
and in the viscera. They are most commonly seen in the subcutaneous tissue over the shoulders and back and are usually multiple, but may occur singly They vary in size from pin head to a large melon, are soft, spherical and freely movable on the underlying tissue, but may be adherent to the overlying epidermis. Subjective symptoms are absent The tumour may be hereditary but is usually found in elderly people and grows slowly They are more common in females. The older tumours may show liquefaction (contents resemble olive oil).

*Histology* Severe damage to vascular endothelium in the cutis, infiltration of round and spindle cells with haemorrhage and cellular disintegration. The lipoids are extracellular with large amounts around vessels, spreading to involve the entire cutis. No foam cells found.

*Treatment*

1. Repeated radiation.
2. Low diet in fat.

*g. Lipoid proteinosis* (Lipoidosis cutis et mucosa) URBACH – generally begins in infancy involving the mucous membranes of lips, mouth



966 Xanthoma with Touton giant cell.

and larynx, later followed by cutaneous manifestations. Hard yellowish infiltration on inner surface of the lips, soft palate, uvula and under surface of the tongue (tongue may have a hard wooden consistency). A child is unable to talk. Tracheotomy may be necessary because of stenosis of the larynx. On the face yellowish nodules can be seen together with variola like scars. A secondary variety of the skin manifestations consists of hyperkeratotic lesions on dorsa of fingers, elbows and knees. There is a definite hereditary tendency and a family history toward diabetes. Blood lipids are essentially normal – or there may be an increase in lecithin.

**OSTEOMA CUTIS (OSTEOSIS CUTIS)**

These lesions consist of bony deposits in the skin and subcutaneous tissue which occur secondarily in certain diseases, *i.e.* syphilis, tuberculosis or as the result of trauma, (even acne has been incriminated). They are most commonly seen on the scalp forehead, cheeks and may







969–971 Bourneville-Pringle's disease in the Negro.

*(Orig. G. Costa–Belo Horizonte)*

be either single and localized or multiple and generalized. Some authorities feel that they are the result of misplaced embryonal germ cells while others favour the theory of metaplasia. Spontaneously occurring osseous deposits in the skin are rare.

*There are two types*

(*a*) Compact (Osteomas durum, eburneum)
(*b*) Porous (Osteoma spongiosum, medullare).
*Treatment* Surgical excision.

## II MUSCLE OR NERVE TISSUE ORIGIN

### MYOMA

*a Rhabdomyoma* is a tumour composed of striated muscle fibers, the occurrence of which in the skin is doubtful.

*b Leiomyoma* (*Dermatomyoma*)

*Multiple cutaneous leiomyomata* arise from the arrectores pilorum muscle and are pin head to pea-sized brownish papular lesions occurring principally on the face, neck and extensor surfaces of the extremities and tending to spread and multiply for years and then coalesce. They are usually painful to a degree according to their size. There is a greater frequency in males (2 times)

*Subcutaneous leiomyoma* are often solitary and deep and usually arise from the dartos muscle (*dartoic myoma*). They are seen usually on the mammae, labia majora, penis and scrotum, developing slowly and varying in size between a small nut to an orange sessile or pedunculated. The colour is reddish-yellow A common variant is the angiomatous leiomyoma. With passage of time they become painful, owing to contraction of the musculature and have been known to become malignant and invasive

*Histology* Consists of smooth muscle fibres with characteristic rod shaped nuclei. The connective tissue sends fibres between the muscle bundles, and elastic tissue is usually seen in young tumours

*c Myoblastic myoma* may be found on the tongue, lips and skin (leg and clavicle have also been reported) and consists of a fibroid nodule of non-differentiated granular cells of varying shape resembling myoblasts which may form cylinders sheathed by connective tissue. They are derived from the embryonal skin muscle plate and are usually benign.

*Treatment* Surgical excision.

#### NEUROMA

*Neuroma* is a tumour composed of non medullated or medullated nerve fibres and connective tissue and which seems to be derived from the sympathetic nervous system. It originates from the neurolemma, grows slowly is usually solitary tender reddish or bluish in colour and agonizing paroxysmal and radiating pain may occur. Patients are all males of middle or advanced age. The lesions are usually located on the shoulders, arms thighs and buttocks Some may become *malignant*, a neurogenic sarcoma.



972. Elephantiasis (*Pantalon de zouave or plus fours leg*) due to neurofibromatosis.

*(Prigs–Jejakarta)*

*Classification* (histologically)

1. Ganglioneuroma (newly formed nerve cells, ganglion cells and nerve fibres).
2. Neuroma myelinicum (medullated fibres).
3. Neuroma amyelinicum – (non-medullated fibres).
4. Schwannoma (perineural or endoneural fibroma) – sheath fibres.

*Treatment*

1. Surgical excision.
2. Gamma irradiation (ANDREWS)

*a Neurofibromatosus–Neurogliomatosus*–VON RECKLINGHAUSEN'S *Disease* consists of a form of congenital dysplasia manifested by developmental changes in the nervous system, muscles bones and skin. It is frequently familial, occasionally associated with mental deficiency muscle weakness or paralysis endocrine unbalance and may be found with or without other types of naevi *i.e.* vascular, verrucous pigmented or hairy naevi or even xanthomata. Concurrence with adenoma sebaceum is not unusual. Onset occurs in childhood or later in life. The chief findings are



973 Rare case of lymphangioma in the axilla.
*(S emens Leyden)*

1 Cafe au lait spots (forme fruste) which may persist without tumour formation.
2 Multiple neurofibromata.
3 Localized sizeable molluscoid growths, frequently pendulous.

There is a slight tendency for VON RECKLINGHAUSEN'S disease to undergo malignant transformation in about 8 % of cases Recurrence after excision of the tumour may occur and these may be dermatofibroma or dermatofibrosarcoma protuberans

*Histology*

A connective tissue new growth of peculiar character which originates in the endoneurium of the nerve trunks in the subcutaneous tissue. The growth is well defined and composed of a gelatinous connective tissue with fine fibers these are spindle shaped and round connective tissue cells with well marked nuclei. The glands of the skin are unaffected except as they are displaced by the new growth there is no elastic tissue within the tumours. Usually there is a narrow band of normal cutis between the tumour and the epidermis.

*Treatment* None is satisfactory but if tumours get too large or are on locations warranting some surgical excision may be carried out. Most lesions, however are best left alone.

*b Glomus tumour* This tumour is an angioneuromyoma and was first described by MASSON in 1924 The tumour is usually but not always encapsulated and as a rule does not metastasize or recur The lesions consist of small rounded pinkish or purplish fleshy nodules usually solitary composed of convoluted vascular channels surrounded by smooth muscle cells among which nerve filaments are intertwined. They are most usually seen subungually on the tips of the fingers though they have been reported on the toes, forearms lateral surface of the thighs, and rarely in the neck. The normal glomus may be caused to proliferate, owing to trauma or disturbances of circulation of the end of the finger Glomus tumours give rise to violent and excruciating pain paroxysmally and on manipulation or trauma. Pin point pressure elicits pain at the exact site of the lesion. Though not proven familial or hereditary multiple cases in one family have been reported

MASSON distinguished three types.

1 Angiomatous.
2. Epithelioid.
3 Neuromatous

*Treatment* Surgical excision is usually curative.

**III. NAEVI**

All of us have naevi ("blemishes" or "marks") of some type that may be present at birth or that more frequently do not appear until infancy or even later in life. The simple classification of the more common types of naevi presented is of great help in differential diagnosis and as a guide to prognosis and treatment.

**A. VASCULAR NAEVI**

*Vascular naevi* as a rule present no diagnostic difficulties but may pose serious treatment problems As they constitute chiefly cosmetic deformities this consideration must be paramount in the choice of therapeutic measures.

*Naevus vasculosus* (Hyperplasia of blood vessels)

1 *Flat* (capillary) – example *naevus flammeus* This lesion should be practically *never* treated, as the results are invariably poor cosmetically Tattooing flesh coloured tints over the area sometimes gives best results

2. *Raised* – examples *angioma spider naevus* Angiomas may partially



974 Haemangioma in a Chinese child from Malaya. *(Fasal–San Francisco)*

or completely disappear spontaneously but frequently do so leaving deep cicatrices depigmentation or other cosmetic deformities that are hard to correct later Therefore, administration of early small, in frequent doses of radium is the procedure of choice because of the good result and freedom of danger from this agent in specialists hands. Freezing is the next best treatment or the injection of sclerosing materials The spider naevus may disappear spontaneously It is best destroyed by electrolysis or an electric needle puncture.

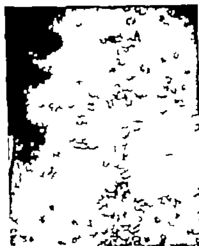
3 *Deep* example cavernous angioma.

These rarely disappear also but the best treatment is radium or the injection of sclerosing materials. Surgical excision may be practiced. Freezing does not destroy the deep vessels

*Naevus lymphangiectodes*

These rare lesions which are more common than the pure naevus lymphangiectodes are made up of a combination of blood and lymph vessels. Spontaneous disappearance is not to be expected.

*Treatment* Superficial cauterization with either cold or hot cautery or at times radiation.



975. Epidermodysplasia verruciformis.
*(Oscar Carla-Bela Herkzenn)*

*Mixed vascular naevus*

Example combinations of the above types in the same naevus.

**B. THE PIGMENTED HAIRY AND WARTY NAEVI**

Differentiation of the lesions in this group frequently presents great diagnostic difficulties that can be solved only by biopsy (by excision) preferably followed by careful study of the sections. Errors in diagnosis, followed by improper treatment, may result in needless cancer deaths. This is not an uncommon experience in the management of this group of naevi and should be avoided at all costs because of the dangers of the malignant melanomas.

1 *Intraepidermal naevus* (no naevus cells)

These lesions rarely may terminate as an epithelioma. Most lesions of this group are slightly raised, verrucous, and have some pigmentation, and but for the unusual bizarre appearance, might be mistaken at times for unusual or linear warts. The so-called seborrhoeic or senile verruca do fall into this group. Another example is the benign pigmented epithelial naevus, which is entirely flat and smooth but has considerable pigmentation. This naevus may readily be mistaken for the junction naevus or even the naevocarcinoma. The chief clinical points of differentiation are the facts that they are nonelevated, never show any sign of change, such as decided change in colour, bleeding, ulceration or the inflammation as seen in a malignant melanoma.

*Histology*

No naevus cells are present. The changes seen in this type naevus are essentially of two varieties.

a) The verrucous type, in which the epidermis is decidedly thickened, may be arranged somewhat in a lace like fashion and contain horny cysts. Some pigment may be present. The palisade margin is usually intact. The upper cutis may or may not show a mild reaction consisting of small round cells.

b) In the second variety, the chief change is an increase in pigment which is entirely in or about the basal cells of the epidermis (the so-called benign pigmented epithelial naevus.)

*Therapy* With the exception of the benign pigmented epithelial naevus, all examples of this group are best treated by desiccation or desiccation and curettement. The benign pigmented epithelial naevus should be left alone, but may be excised for diagnostic purposes. Radiation is contra indicated for all examples of this group. Freezing may be done but is not as desirable and requires expert selection and technique.

Typical examples of this group

1 Naevus verrucosus (hard) – hairs or pigmentation may also be present. A linear configuration is common.
2. Benign pigmented epithelial naevus
2. Seborrheic verruca or verruca senilis or keratoma senile – commonly seen on the trunk and face.
4 Dermatosis papulosa nigra – found only on the face of Negroes, Filipinos, etc.

2. *The Junction (Epidermo-dermal) naevus* (naevus cells present)

This is the only lesion of this group that may terminate as naevocarcinoma (malignant melanoma), the most dangerous of all types of cancer. Fortunately this occurs extremely rarely when one considers the great frequency of the lesion. Junction naevi which appear at or about birth or earliest infancy appear to have a lesser degree of malignancy than those arising suddenly later in life. They grow more slowly, metastasize less rapidly and may be cured by early intervention if a change to nevocarcinoma occurs. Contrasted with



976 Dermatosis papulosa nigra.

*(F [illegible]-San Francisco)*

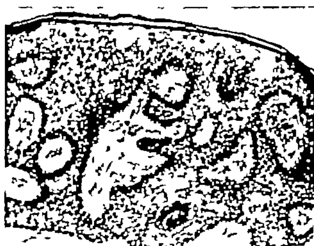
this type is the Junction naevus that appears later in life, grows more rapidly and when it becomes a naevocarcinoma has an extremely bad prognosis as metastasis is early, rapid and a fatal outcome occurs within a few months to one or two years.

Characteristically the junction naevus may occur anywhere on the body, is usually smooth, small, relatively non warty and generally is devoid of hairs. Junction naevi, however, do not all run true to form and various types of exceptions to the above description may occur

*Histology*

Naevus cells are present and arise at the epidermo-dermal junction. There may be a large amount of pigment both within the epidermis and the upper cutis. Areas of segregation or theque formation may be present. A mild inflammatory reaction is sometimes seen.

*Therapy* Because of this and the fact that mixed lesions do occur relatively frequently it is often difficult to make a clinical diagnosis with certainty therefore all doubtful lesions should be removed by excision, both for diagnostic purposes and also because excision either with a scalpel or by the electric cutting current is the treatment of



977 Dermatosis papulosa nigra.
*(Fasal-San Francisco)*

choice Radiation, freezing and all chemical methods of removal are contra-indicated.

Example *Naevus pigmentosus* – may rarely present a few fine or sparse coarse hairs or have a soft warty surface.

3 *Intradermal naevus* (naevus cells present)

The intradermic naevus of so-called *"common mole"* always remains benign if of pure type (not a mixed lesion). The intradermal naevus is found much more commonly on the face than elsewhere on the

body usually from the age of 20 upward. It may easily be destroyed by electrolysis, desiccation, or by excision. It will not recur if destroyed only to skin level.

*Histology*

Naevus cells are present. These are arranged at a depth in the cutis in the shape of strands, bands or whorls. Pigment is present in a varying degree and hair follicles



978. Widespread verrucous pigmented naevi. On the lower arms some amelanotic (*i.e.* non-pigmented) papules.

*(Prayt-Jayakaria)*

are frequently found. There is a clear zone about the upper cutis and there is no activity at the epidermo-dermal junction. The epidermis shows no significant changes.

Example *naevus pigmentosus et verrucosus et pilosus* – soft warty not hard and either flesh coloured, pigmented and with or without hairs.

4 *Blue naevus* (naevus cells present)

The naevus cells are stellate shaped rather than round or oval as in the preceding types The blue naevus may rarely terminate as melanosarcoma is slate black or blue-black and is frequently mistaken for a junction naevus or naevocarcinoma. It is a benign lesion as only in the rarest instances has it been reported as terminating as melanosarcoma. Characteristically the colour is blue-black, slate black or brownish-black. It is located deeply in the cutis and the peculiar blue colour is reflected through the upper layers of cutis and epidermis. The lesion is best left alone. If the lesion is in an area subjected to extreme trauma, or if diagnostic difficulties arise, excision is the procedure of choice.



979 Benign lentigo.

Radiation, freezing or chemical methods of destruction are definitely contra-indicated

*Histology*

Naevus cells are present, located usually at a depth in the cutis. They are stellate shaped and are of an entirely different appearance than the naevus cells seen in the junction or intradermic naevus A considerable amount of pigment may be present in the upper cutis.

5 *Mixed pigmented hairy or warty naevus*

The combination or mixture of two or more of the above types occurs with relative frequency Thus the prognosis of such a lesion depends

on the type of naevus present and it is possible to have such lesions terminate as epithelioma, naevocarcinoma (melanoma or melanosarcoma). As a rule it is impossible clinically to recognize mixed types and it is only following microscopic examination which should be practiced in all doubtful lesions that they may be identified. Naevi *may also be associated with epitheliomas that do not actually arise at* the expense of the naevus.

## C. NAEVI OF SPECIAL TISSUE

Fortunately naevi of special tissues are extremely rare. They are usually recognized only and catalogued after microscopic examination, as most



980 F broom-like tubercles in lepromatous leprosy

*(Osw G Costa-Belo Horizonte)*

of the lesions appear clinically as small tumours. This is particularly true of this group. The diagnostic excision, which in most instances can be performed so as to remove the entire lesion, is the treatment of choice.

1 *Glandular* (Sudoriparous gland naevus).
   (Sebaceous naevus).

2. Connective Tissue Naevus
3. Fat Tissue Naevus – naevus lipomatodes.
4. Nerve Naevus
5. Mixed Types.

*Histology*

*Mixed type naevus* The histopathology of this lesion is that of any of all of the above types found in the lesion.

## IV TUMOURS OF INFECTIOUS ORIGIN

These very common epithelial growths which are characterized by a papillary proliferation (acanthosis) are caused by a filtrable virus. This



981 Hornified verrucae vulgares.
*(Orig. G. Costa-Belo Horizonte)*

is certainly true of all types but has not been proven for the seborrhoeic wart. The lesions are auto-inoculable. It is not known whether the various types of warts are caused by the same virus differing in virulence or altered in their growth reactions because of their different anatomical locations thus varying the clinical picture or whether each type is caused by a special virus. The behaviour of warts is most peculiar in that they may be most rebellious to all types of therapy or may disappear spontaneously or by auto-suggestion. Why tumours caused by a virus can be made to disappear by suggestion is not understood.

All types of warts with the exception of the seborrhoeic warts, occur in children or young adults. Seborrhoeic warts or seborrhoeic keratoses are found most commonly in individuals over forty years of age. None of these lesions are prone to give rise to malignant change.

## A. VERRUCAE

1 *Verrucae vulgaris* or common warts are usually found on the hands fingers, occasionally on the forearms, knees, face, scalp or elsewhere. They are quite common about the nail folds, a location where it is difficult to treat them without pain and disfiguration. They are usually grayish in colour pin head to pea sized or larger, with a rough warty surface. They may be discrete or confluent, forming plaques in which painful fissures may occur especially in winter If not completely destroyed, regrowth in situ may occur

*Histology*

*Verrucae Vulgaris* characterized by acanthosis and hyperkeratosis with considerable proliferation of the rete ridges so that the papillary bodies seem to radiate directly the center there is vacuolation of many cells in the prickle cell layer and in the granular layer where some shrivelling of the nuclei is seen. Parakeratosis is also seen and mitotic figures are seen especially in the basal layer Similar changes are seen in *verrucae planae juveniles* and *verrucae plantarum* differing basically only in degree

*Treatment* Desiccation, curettement, chemical applications, surgical removal radiation, freezing and psychotherapy are the methods of treatment. The response to radiation is about 65 % some warts failing to respond regardless of the quality or quantity of dosage. The highest percentage of cures over 95 % results from desiccation and curettement but frequently tiny scars may be left by this procedure. The advantage of radiation is that it is painless no dressings are required and there is usually no scarring Acid treatments must be carefully controlled and the patient must not be permitted to carry this out because of the bad scarring and frequent keloid formation that may result. The chemicals usually used are glacial acetic acid, nitric acid, trichloracetic acid or podophylin. Freezing with solid carbon dioxide is painful and has no particular advantage over desiccation or radiation.

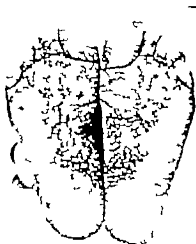
2 *Verrucae planae juveniles* are usually found on the face, dorsa of hands and forearms. They are frequently seen in linear configuration as a

result of scratching and auto inoculation, as these lesions are sometimes slightly pruritic. They are pinhead sized, dirty gray to brownish coloured, slightly raised, smooth shiny papules. They are often extremely rebellious to treatment.

*Treatment* In children under twelve, a few small doses of x rays make them disappear Desiccation should only be carried out with the greatest care because scarring is to be avoided at all costs $^1/_8$ or $^1/_4$ grain prot iodide of mercury tablets, given t.i d.p c. occasionally is successful, as are injections of mercury bismuth or arsenic. Local



982 Verrucae vulgares



983 Plantar warts.
*(Orig G Costa-Bela Herzogpraxis)*

applications of half strength Vlemincks solution, formaldehyde, lotio alba, or 1 mercury bichloride solution several times daily may help Wart vaccine is successful in this type of lesion.

3 *Verrucae plantarum* are found on the plantar aspect of the foot and toes They may be discrete, single lesions but more often they are multiple and may form large plaques in which case they have been called mosaic warts The surface is slightly elevated and warty or may be like a callus with a great deal of the growth downward rather than upward. Depending on location pain may be a common complaint due to the pressure on the nerve ends It is sometimes difficult to differen

tiate these lesions from ordinary calluses. This can usually be done by removing the horny layer and scraping it with a sterile knife or curette until papillary bleeding points appear

*Treatment* Most satisfactory results are obtained from radiation therapy but here again there are about 35 % failures. The advantages however, as so obvious that radiation should be given first choice as there is no incapacitation. The lesions may be reduced in size through the application of a 40 % salicylic acid plaster and paring them down with a sharp knife. Desiccation and curettement may then be carried



984 Verrucae planae juveniles.

out, but healing is usually slow and the wound may be slightly painful. Single cautery puncture to center of wart, destroying blood supply may eliminate the growth. The large mosaic warts should be treated with 40 % salicylic acid plasters and intramuscular injections of bismuth, usually from twelve to twenty injections of bismuth are necessary to effect a cure which occurs in approximately 50 to 75 per cent. of the cases.

4 *Verrucae filiformes* These small threadlike and pedunculated flesh coloured or light brownish lesions are usually found growing on the

neck, eyelids, anterior axillary folds, face, especially about the nostril. Individual lesions present no great problem in treatment as they may be snipped off with a sterile scissors and the base cauterized or the entire lesion may be desiccated. However if they occur in the bearded area, shaving may spread them in such a way that successive groups appear and one merely gets rid of one group before another appears. These lesions do not respond well to radiation.

5 *Verrucae progenitales or verrucae acuminata* are gray bluish or pinkish filiform warts that grouped together form cauliflower like growths. In women extensive areas of the vulvae may be involved with the pro-



985. Radiation ulcer following maltreatment of a common wart with radium.

*(Simons–Amsterdam)*

duction of large vegetating masses, having a foul smelling exudation. They are found most commonly on the penis, vulva, perianal and perineal regions The predisposing causes are uncleanliness, friction, discharges gonorrhea and pregnancy

*Treatment* The treatment should be improvement in cleanliness and hygienic care of the affected parts mild antisept washes and a dusting powder containing 33 % calomel. Discrete s lesions may be destroyed by application of podophyllin, a silver stick or tri chloracetic acid or desiccation. Extensive cases r respond rapidly to treatment with X rays

6. *Seborrhoeic verrucae or seborrhoeic keratoses* perhaps rightfully do not belong in this category as *their infectious nature has not been proven.* However there seems to be little doubt but that they are auto-inoculable as they occur abundantly in the moist area under the breasts and elsewhere on the trunk where the factor of infection from one site to another seems obvious. While they are most predominantly found on the trunk, they occur with frequency on the extremities face and scalp. The lesions are *elevated soft verrucous and vary extremely in*



886 Condylomata acuminata of the eyes may occur in their absence on the genitals.

*(Siemens—Amsterdam)*

color from a light brownish to a dirty brown or black so that they have occasionally been mistaken for a malignant melanoma. Rarely the lesions may reach an enormous size but only 2 % or less undergo malignant change despite their great frequency in older individuals.

*Treatment* Unless the lesions become large in size or are in areas subjected to constant trauma, treatment is unnecessary as they are benign. Radiotherapy is not effective but they may be easily removed by desiccation or curettement. They are most frequently removed for cosmetic reasons.

## B. MOLLUSCUM CONTAGIOSUM

*Molluscum contagiosum* as the name implies, are lesions that are quite infectious and are easily acquired in playgrounds, schools swimming pools and in the exchange of clothing The incubation period is from six to twelve weeks The lesions are usually found in children, less frequently in adults They appear anywhere but are most commonly seen on the trunk buttocks rarely on the face and eyelids The lesions consist of small discrete, pearly or waxy globular flesh coloured tumours with umbilicated centres They vary from pin head to pea-



987 Umbilicated mollusca contagiosa.

sized growths Unless secondarily infected, there is usually no surrounding inflammation.

*Histology*

*Molluscum contagiosum* microscopically composed of multiple closely packed pear shaped lobulated nodules composed of epidermal cells individual lobules are separated by connective *tissue fibers. The gross central umbilication* is microscopically caused by a crateriform depression which is covered by horny lamella. Basal cells comprise the outer layer of each lobule In the center of the lobules are located the molluscum bodies which are large oval dyskeratotic cells containing granules

*Treatment* The entire body must be carefully examined so that all

lesion may be destroyed to prevent reinfection and it is also well to sterilize clothing Individual lesions sometimes will disappear simply from needle puncture or as a result of a superficial incision through the roof of each lesion, expressing the waxy contents. A sharp curette also readily removes these lesions without scarring



988. Umbilicated papules of molluscu contagiosum.
*(Piers–Nairobi)*

## C. GRANULOMA PYOGENICUM

This fairly common tumour which may be found arising from the skin or mucous membrane, results because of a peculiar reaction to the presence of pyogenic bacteria, usually following trauma. They are usually single, dull red or purplish-red nodules or tumours, sometimes pedunculated, varying in size from a pea to a hazelnut. They are found most commonly on the fingers, face, lips, scalp and trunk. They have a tendency to bleed easily on the slightest trauma and if not completely removed or destroyed, they tend to recur rapidly frequently giving rise to the mistaken conception that the lesion is a malignant one. Their growth at first is rapid, but later they become stationary after reaching a certain size The lesion is a granulomatous reaction to trauma plus infection with the staphylococcus aureus.

*Treatment* Treatment consists of electro-desiccation or cauterization.



989 Granuloma pendulum or botryomycoma on the inside of the lower lip.

*Histology*

*Granuloma pyogenicum* typically it is like a nodule with newly formed capillaries and blood vessels traversing narrow neck or pedicle and then dilating and proliferating within the tumor The blood vessels are superficially located and this accounts for the ease of bleeding on trauma. There is an infiltrate of mast cells and polymorpho-nuclear leukocytes, plasma and small round cells and later fibroblastic proliferation Numerous micro-organisms have been found including streptococci, B. coli, Proteus vulgaris. No mitoses are seen.

**D MILKERS NODULES**

Cattlemen and slaughterhouse employees occasionally develop an infectious disease from cow udders that is caused by the vaccinia virus. The infected cows generally present vesicles on their teats. A few days after exposure inflammatory slightly pruritic papules, develop on the hands, wrists or forearms and within a week these become pea-sized or larger hemispherical bluish-red, firm nodules. The centre of the nodule becomes brownish, flattened and umbilicated. Occasionally a small crust or vesicle forms in the central portion and there may be a little purulent exudate followed by the growth of bleeding reddish papillomatous vegetations. Lymphangitis and adenitis may develop. The milkers nodules very often resemble progenic granulomas. They usually start as a single lesion in a scratch and about this usually two or three other nodules develop in close proximity The disease is self



990. Milkers nodules.
*(Sammers–Leyden)*

limited and tends to clear up of its own accord in about six to ten months.

*Histology*

The milker's nodule consists of granulation tissue with mononuclear and epithelioid cells or variola-like multilocular vesicles with intercellular edema and eosinophils. Sometimes they have been reported to resemble verrucae.


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CHAPTER 97

# MALIGNANT TUMOURS OF THE SKIN

## Introduction and Aetiology

R. E. J. TEN SELDAM – Sydney
JOHN C. BELISARIO – Sydney

## Symptomatology and Therapy

JOHN C. BELISARIO

## Pathology

R. E. J. TEN SELDAM

### INTRODUCTION

Malignant tumours are now recognised to occur in all climates and amongst all the different species that compose mankind. Up till fairly late in this century it was thought that malignancy was only rarely found in the Asiatic and African people, but the gradual extension of medical help in the Western sense of the word, going hand in hand with growing confidence of the native populations of less developed countries in modern medicine taught otherwise. However differences in frequency of occurrence of different types of malignancy were successively established.

The high incidence of primary carcinomata of the liver in Indonesians and Chinese (SNIJDERS and STRAUB) and similar findings in the Bantus of Africa (GILLMAN BERMAN) is one example. The near absence of primary stomach cancer in Indonesians (BONNE, Year Reports Netherlands East Indian Cancer Institute 1929–1941) is another. More could be added. The cancers of the oral mucosa due to betel-nut chewing in India and Indonesia (ROOS VAN DEN BERGH) is another example. So is the old example of the "*kangri burn*" cancer in Kashmir (NAPIER).

It was thought, however that the deeper pigmentation of Oriental and African races would prevent the common occurrence of carcinomata of the skin owing to the protective influence of this pigmentation against the deleterious effects of the ultraviolet component of the sunlight.

The relative rarity of malignant melanoblastomata observed in North American Negroes also seemed to indicate a lesser susceptibility at least of Negroes to developing that kind of malignancy of the skin. How erroneous it may be to draw conclusions from such observations will become self-evident.

Among the Whites in the tropics malignant tumours of the skin are rela

tively infrequent as many of them return to their country before reaching the "tumour age" (TEN SELDAM, SIMONS) while also, owing to their ways of life generally, their skin is less exposed to the damaging influence of too much ultraviolet rays (TEN SELDAM). Other possible causes for cutaneous carcinoma like chronic ulcers on the legs and feet or repeated trauma on these parts, burns etc. also play a negligible rôle in Europeans in the tropics as compared with the native population. However, where a white population is doing manual labour under tropical conditions, this is different, as for example among the white fishing population of St. Martin where carcinoma of the face is of more common occurrence (WINKLER).

The microscopical appearances of cutaneous neoplasms are the same in the tropics as in temperature climates but many growths are more anaplastic. Despite this fact metastases are not so frequently encountered (TEN SELDAM, STRONG) and it is sometimes remarkable what extensive carcinomata can be encountered still without any demonstrable metastases (TEN SELDAM).

Cancer statistics in the tropics have not generally been very reliable, not only owing to poorer facilities for treatment and diagnosis, but also owing to few doctors usually being present for the sometimes large populations and the vast areas these physicians have to cover. Also a lower expectation of life, owing to obvious causes such as malnutrition, lack of hygiene, combined with a high prevalence of all kinds of infectious diseases, lessens considerably the number of people who reach the cancer age.

## INDONESIAN STATISTICS

Skin carcinoma in Whites occur most commonly on the head. Statistics from the "Antoni van Leeuwenhoekhuis" (Dutch Cancer Institute) at Amsterdam show 87.7 per cent. of 810 skin cancers to be localised on the head (face, ears, scalp). To these might be added 47 cases originated in lupus vulgaris (WASSINK). MAGNUSSON mentions that in his cases only 40 or 4.45 per cent. of 899 were *not* localised on the head. These are only two examples to which many could be added. The findings amongst Indonesians are completely different, as VOS first pointed out. In his statistics only 46.8 per cent. were localised on the head. Later figures from the same Instituut (Netherlands East Indian Cancer Institute, TEN SELDAM) give a similar figure (35.5 per cent. of 893 cases localised on the face and ears and 45.1 per cent. for the whole head).

The majority of cases not localised on the head occurred on the lower limbs, especially the lower leg and foot (see Table I).

TABLE I

| Localisation | Holland (± 20 yr) | | Bandung (6½ yr) | | Bandung (14½ yr) | |
|---|---|---|---|---|---|---|
| Face (c. naso et palp.) | 621 | 85.5% | 160 | 37.7% | 301 | 35.5% |
| Ears | 72 | | 10 | | 16 | |
| Scalp | 17 | | 41 | | 86 | |
| Reg. colli et nuchae | 11 | | 15 | | 45 | |
| Reg. axill. et inguin | 2 | | 4 | | 13 | |
| Ca. in lupo | 47 | | — | | — | |
| Trunk | 18 | | 40 | | 76 | |
| Arms | 3 | | 9 | | 21 | |
| Hands | 10 | | 7 | | 12 | |
| Upper legs | 4 | | 13 | | 19 | |
| Lower legs | 5 | 0.7% | 95 | 33.7% | 220 | 34% |
| Feet | 0 | | 57 | | 84 | |
| Total | 810 | | 451 | | 893 | |

Lupus vulgaris is extremely rare among Indonesians if it ever occurs. This explains the complete absence of carcinoma in lupo in this table.

The high frequency with which cancers of the lower leg were observed is self-evident.

These carcinomata do not usually develop quickly and suddenly. Sometimes a chronic ulcer has been present for many years before malignancy supervenes.

Also strong clinical suspicion of a carcinoma may exist without histological support.

As no compulsory registration of births existed for Indonesians, all dates related to their age are estimations. They were derived from forms accompanying material sent to the Netherlands East Indian Cancer Institute for histo-pathological inspection by various doctors from all over Indonesia. It was still worthwhile to compare the groups as far as possible for the two main localisations (see Table II).

TABLE II

| Age | Skin carcinoma (crus et pes) | | Skin carcinoma (facies, cranium) | |
|---|---|---|---|---|
| 11–20 years | 5 | | — | |
| 21–30 " | 33 | | 11 | |
| 31–40 " | 97 | | 60 | |
| 41–50 " | 88 | | 121 | |
| 51–60 " | 59 | 23.9% | 119 | 45.1% |
| 61–70 | 9 | | 29 | |
| 71–80 " | 1 | | 9 | |
| 81 | 1 | | 1 | |
| Total | 293 | | 350 | |

From this table it is clearly evident that, as a group, *the carcinomata of the leg are encountered far more in the lower age-groups*. That the carcinomata of the face and head generally would fall in the higher age groups was to be expected from experiences in Europe, America and Australia. This difference in age groups strengthens the opinion expressed further on in this article, that the predisposing causes for skin carcinoma of the leg and those of the face and head are at least partially different. This also explains partially why carcinoma of the face seems to be less common in Indonesian people than in Whites in a temperate climate, as the older age-groups amongst Indonesians will form a smaller percentage of the main population than is the case in medically more advanced countries, as explained earlier in this chapter.

The carcinomata of the face were subdivided in the two main histological types (Table III).

TABLE III

| | Face (including nose and eyelids) | |
|---|---|---|
| | Squamous cell carcinoma | Basal cell carcinoma |
| Indonesian men | 64 (37.9%) | 105 (62.1%) |
| Indonesian women | 44 (33.3%) | 88 (66.7%) |
| Total | 108 (35.9%) | 193 (64.1%) |

Though formerly (TEN SELDAM) a separate group was formed for the metatypical forms, these are now included in the group of basocellular carcinomata for reasons explained further on. The findings showed a difference when compared with statistics from elsewhere. *These statistics accepted about 70 per cent. of the carcinomata of the face to be basocellular in type and 8–15 per cent. of metatypical structure* (DARIER and FERRAND 15 per cent., OWEN 13 per cent., BUTLER and MORELLI 8.5 per cent., MAGNUSSON 8 per cent.). If these were included in the group of basocellular carcinomata, that group would form about 80 per cent. as compared with about 64 per cent. in Indonesian people. This difference could be explained by statistical error through too small numbers, though the chance that this be so would be less than 1 : 200. Another possibility is that basal cell carcinomata develop usually in a slightly higher age-group and, for reasons given, this particular group will be comparatively smaller in Indonesians. It is, however, also possible that other factors play a role. The figures, though small, seem to be suggestive enough to warrant further research.

## "PRECARCINOMATOUS" CONDITIONS

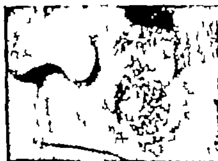
The tendency of carcinomata to develop in conjunction with certain pre-

existing pathological conditions has lead to the recognition of the following as possible or probable precursors

*Keratoses* (solar, arsenical and occasionally senile or presenile seborrhoeic). *Xeroderma pigmentosum. Cutaneous burns. Cicatrices. X-ray and radium dermatitis or ulceration. Chronic actinic dermatitis* (sailor's farmer's skin). *Occupational hazards e.g.*, paraffin, arsenic, scars, heat, sunlight, soot, coal tar, embedded foreign bodies. *Leucoplakia. Lupus vulgaris. Lupus erythematosus. Chronic ulcers*, etc.

## PREVALENCE

Approximately 50 per cent. of all carcinomata are found on the skin (BULL



991 Squamous cell carcinoma on lupus erythematosus.

and HANSEN). They are more common per head of population in Australia than in other parts of the world (BELISARIO) and ten times more so than in Great Britain (MOLESWORTH). ROSANOVE stated that approximately 14 per cent. of almost 5000 cases of skin disease between 1912 and 1951 in Melbourne (Victoria) were cutaneous malignancies. They are commonest in sub-tropical climates.

## ASSOCIATED PREDISPOSING FACTORS

### 1 Age

Cutaneous carcinomata commonly appear in the latter half of the life cycle mostly around the ages of 45 to 50 years, but cases have been reported in adolescents. One of us (B) has observed a basal cell carcinoma in a boy 15 years old and SCHARNAGEL and PACK reported multiple lesions in a child at five. They are common in young children with xeroderma pigmentosum, a hereditary and sometimes familial condition (BELISARIO) and characterized by a congenital hypersusceptibility to ultraviolet rays probably owing to some deficiency of the skin protective mechanism.

**2. Sex**

The incidence of carcinomata is generally greater in men than in women particularly on the lower lip (10 to 1) (MOLESWORTH)

**3. Heredity**

Doubt still exists as to whether heredity plays any direct part in the occurrence of skin cancers. It does, however appear to exert an indirect influence by providing a suitable pabulum for their growth (ELLIOTT and WEBSTER). Individuals who are blond and fair-skinned, or who have red hair ruddy complexions and skins which freckle rather than pigment and tend to be harsh and dry show a much higher incidence of skin carcinomata than those with dark and often oily skins A low actinic tolerance on exposure to wind and sunlight is probably another manifestation of hereditary influence. Blue eyes are found more frequently in those indi-



992. Ulcerating squamous cell carcinoma and hyperkeratosis in a man with yaws.

*(Netherl. East Ind. Cancer Inst.)*

duals whose skins are lacking in pigmentary protection from the sun's rays, and brown eyes in those with natural pigmentary protection (MOLESWORTH, BELLS and H[illegible])

**4. Sunlight**

Attention has been drawn to the large part played by sunlight in cutaneous cancer by LAWRENCE PAUL, MOLESWORTH, PIERS and others Cutaneous carcinomata commonly arise on solar keratoses but may also do so independently In Australia solar keratoses occur more commonly than any other skin condition and thus predispose to the frequent incidence of cutaneous carcinomata Exposure to the ultraviolet rays of the solar

spectrum and lack of protective pigment in the skin of a people predominantly of British descent, assisted by the habit of sunbathing and working outdoors in shorts and no shirt, are the main predisposing factors (BELISARIO) Individuals with olive skins are less affected than those with fair skins yellow-skinned races are affected still less and those with black skins still less again.

Industrial and arsenical keratoses are rare but play a contributory rôle in initiating skin carcinomata. Keratoses may be single but are commonly multiple. Areas of



993. Tropical skin with solar hyperkeratoses and carcinomata.
*(Simons Amsterdam)*

predilection are the face, ears, neck, backs of the hands and forearms. One of us (B) has not observed solar keratoses on the palms or the bathing trunk area but has seen squamous cell lesions arising on these areas "de novo" and an occasional basal cell lesion on the latter area. Hence it is evident that sunlight is not the only factor concerned. In this respect HODGSON reported a case of *carcinoma of the anus* following the use of a tar solution for eleven years for pruritus ani. This was obviously no sunlight effect. In Indonesians cancer of the buttocks and around the anus have sometimes been seen (TEN SELDAM).

Apart from the many clinical observations experimental support has been given to the opinion that sunlight, and especially the ultraviolet rays plays an important rôle in the aetiology of keratoses and skin cancer.

*Colquhoun described the case of a man of 27 who developed severe keratoses of the solar type after repeated U.V. radiation over a long period, given him by a quack. Cutaneous papillomata in the rat and also carcinomata were induced with U.V. radiation by Findlay. Roffo also induced malignant tumours in the skin of experimental animals through U.V. radiation. Both sarcomata and carcinomata developed in the skin and eyes of rats similarly treated by Beard, Boggess and von Haam. The experimental proof that sunlight itself could act carcinogenically was given by Rusch, Kline and Baumann. Other examples could be given (Coblentz).*



994 Betel nut carcinoma.

(*Prins–Djojokarto*)

For the development of *cancer of the lip* the influence of the sunlight seems to be marked also. It seems highly significant that cancer of the lip affects mostly the lower lip (the one most exposed to sunlight) and that cases of indoor workers are few as compared with those of outdoor workers. It is however remarkable that the few cases of indoor workers occur practically always in smokers and that is so too for most of the outdoor workers. For this reason it is considered that smoking habits might play an additional rôle.

It is possible that a degree of protection from the sun's rays afforded by the use of lipstick by women may account in some degree for the preponderance of lip cancer in males (Molesworth).

Skin carcinomata due to exposure to sunlight over long periods may take from ten to twenty five years to develop. In the tropics they are not seen with the same frequency as in sub-tropical areas even in light-skinned races who endeavour to protect themselves with hats midday siestas and proper clothing from the greater heat of the sun.

It is thought that fair-skinned individuals absorb ultraviolet rays of less than 3000 A through their skin and obtain some protection by a thickening of the horny layer.

Carcinogenetic wavelengths lie between 2900 and 3341 A. Data obtained from the United States of America weather bureau indicate that the decisive factor concerned in the production of carcinomata is the number of sunshine hours and not so much the intensity of each exposure (Elliott and Welton) although the degree of brightness of the sun and reflection from surrounding surfaces such as the sea or snow can play a contributory rôle.

In dark-skinned races pigment is present in the outer layers of the epidermis besides the basal layer, whereas, in Whites, pigment is present almost entirely in the basal layer. *Thus Negroes are found to be about ten times less sensitive to sunlight than Whites as a whole.*

Cutaneous neoplasms occur less frequently in North Africans than in Europeans and are mainly localized in the skin (Montpellier and Mussini Montpellier). They have also been found to be rare in the Solomon Islands (Wechsler).

New Guinea natives show little tendency to develop skin carcinomata by comparison with whites and this difference between dark and light-skinned races appears to obtain in tropical, sub-tropical and cold climates generally (Belisario).

There is, however, a wide scale in pigmentation and it is wrong to consider "white" as opposed to "brown" or "black". Even though the pigmentation of the skin certainly appears to provide some degree of protection from the carcinogenic influence of U.V. radiation, the amount of protection would be very difficult to estimate in a certain race or given individual. It would appear also that the number of sun-hours, in combination with the intensity of the U.V. present in the sunlight, counteracts completely or partially the defence mechanism of the pigmentation present. In relation to this, it is interesting to note that Vaty found that the amount of U.V. in tropical coastal areas was much higher than in European coastal areas and about equal to higher levels (for instance Davos, Switzerland). But he also pointed out that the number of sun-hours in the tropics is much more than in Europe. In Batavia (Jakarta) for instance, the number of sun-hours is greater than 1.5 times that in Amsterdam (2326 as compared with 1492, Vaty). The horizontal plane illumination at Bandung, Indonesia (about 2600 ft. above sea-level) is higher than in Davos (Switzerland), even though the average length of the days is shorter and Davos is more than twice the height above sea-level (Clay and Clay Jolles).

For those reasons it would be important to have similar data available for all kinds of tropical regions. The higher incidence of skin cancer amongst the Balinese

for instance, might well be explained in this way (NOOSTEN) though NOOSTEN also pointed out how the Balinese shun the strong sunlight less than the Javanese, due to the differences in their habits.

*It would appear obvious that the ultraviolet rays comprise the main known predisposing factor of the solar spectrum for cutaneous carcinomatosis since blacks would be more affected than whites if heat were concerned and ships' stokers would be more affected than deck-hands which is not the case*

**5. Arsenic**

Arsenic in small therapeutic doses over a prolonged period or in large doses, ingestion of arsenic in contaminated food, inhalation or external contact in industry may produce keratoses in susceptible individuals. These lesions are commonly symmetrical on the palms and soles but may occur elsewhere. Lesions may develop within a month after a first injection or not until thirty years after administration has ceased. Keratoses commonly persist and 20 per cent progress to carcinomatous changes (ORMSBY and MONTGOMERY SIMONS).

**6. Industrial Influences**

Precancerous keratoses may follow contacts with the carcinogenetic fractions of certain oils or coal tar its distillates and products aniline dyes, benzine soot, paraffin and the like. Subsequent carcinomata are usually squamous in type.

**7 X-Rays and Radium Rays**

Precancerous keratoses and carcinomata ha occurred in operators and techni cians not properly protected from these rays, mainly on the hands and fingers. BELISARIO has found, like ANDERSON that ensuing carcinomata may be basal or squamous cell in type according to the areas where they commonly occur

**8. Trauma**

It is generally believed that frequent trauma o chronic irritation, *e g* chronic ulceration, friction or an embedded foreign body may initiate cancerous changes particularly in a predisposed site.

A single trauma sometimes may initiate changes which, in the long run, lead to the dev lopment of carcinomata. Formerly squamous cell carcinomata have been described developing in fistulas due to shotwounds, but these are to be looked upon as of the same order as carcinomata developing in fistulas of a different origin. It was the chronic inflammation, rather than trauma, which led to the development of these carcinomata. It is still dubious if a single trauma *as such* can directly lead to the de lopment of skin carcinoma (TEN SELDAM). This seems, however to ha e been observed by SPILZINGER and BOROJOVITCH

K loids, following burns or scalds particularly may also be the site of subsequent carcinomatous changes. Trauma appears to play a larger part in the tropics than elsewhere in the initiation of cancerous conditions in nati es, particularly on the feet and legs, where scratches, abrasions and pricks are common on these unco ered areas (DO AND and HOLMES, TEN SELDAM)

Here again it is not the single tra ma as such but the resulting cond tion that ultimately can lead t carcinoma It is well to keep in mind that relatively slight

traumata in native people sometimes can lead to extensive and chronic ulcers. This seems not only to be due to the unhygienic conditions under which they live and easily contract infections, but also to a complete absence of any knowledge of hygiene. Personal experience of one of us (TEN SELDAM) in P.O.W. camps in Indonesia during the Japanese occupation, showed also that in a quantitatively and qualitatively underfed white population, extensive ulcers easily developed after apparently negligible traumata, such as slight scratches or abrasions. In this instance knowledge of hygiene and competent medical advice were not lacking. It seems therefore reasonable to accept the fact that malnutrition may play a rôle in the development of these chronic conditions. Infectious diseases may constitute an additional influence (malaria, yaws, filariasis, etc.).

The importance of yaws might be stressed particularly for the development of squamous cell carcinomata on the lower leg. It is well known that squamous cell carcinoma has been repeatedly observed as developing in syphilitic scars on the tongue and elsewhere. Whereas syphilitic ulcers and scars on the leg in whites are rare in comparison with varicose ulcers and scars, carcinoma developing in syphilitic changes on the leg, though rare, is more common than in varicose conditions. It might well be that a disease as closely related to syphilis as yaws, would lead to similar predisposing changes. There seems to be support for this theory from clinical observations. Carcinoma supervened with remarkable frequency on a previous yaws lesion (BONNE, TEN SELDAM), and repeatedly pre-existing yaws changes were observed in patients with squamous cell carcinomata. It might well be possible that some rare localisations of squamous cell carcinomata (on the buttocks for instance, or around the anus,) were due to pre-existing framboesia. It is highly speculative but not unreasonable to associate part of the high percentage of squamous cell carcinomata on the face of Indonesians (see Table III) with the same cause.

## 9 Miscellaneous Skin Manifestations Associated with Malignancy

*a) Acanthosis Nigricans*

This condition has been found to be associated with malignancy of internal organs in approximately 50 per cent. of cases (SOMERS, OLLENDORF CURTH). The benign type commences in childhood or at puberty and finally becomes arrested or regresses. This type may be familial.

The type associated with malignancy most commonly occurs in middle or old age and cutaneous changes are marked and may show some exacerbation when malignancy supervenes. This type is not familial.

*b) Dermatomyositis*

Cases of this disease occurring in association with internal malignancy have been reported (BEZECNY, DOSTROVSKY and SAGHER, CURTIS *et al.*, FORMAN, CASTELLO, ALLINGTON)

*c) Cheilitis Glandularis*

The occurrence of a squamous cell carcinoma on the lower lip in four cases of cheilitis glandularis in this area has been reported by MICHALOWSKI

## 10. Basic Mechanisms

Though several underlying causes or possibilities of such have been mentioned, the basic mechanism of a developing malignancy has not been dis

cussed. It seems however neither opportune nor the right place here to discuss in detail the many and varied theories and facts. Those interested are referred to the text-books and special journals devoted to this subject.

## MALIGNANT TUMOURS ARISING FROM THE EPIDERMIS

### BASAL CELL CARCINOMA

*Symptomatology*

These lesions appear to originate from the hair follicles sweat glands or down growths of the surface epithelium. The classical feature is the pearly or waxy papule which may be visible throughout the surface of a lesion but is found almost invariably at the edge giving it a "rolled" appearance. The lesions generally more particularly their edges, are apt to be traversed by minute blood vessels. Clinically nine different varieties may be distin-



995 Cystic basal cell carcinoma



996 Pigmented cystic basal cell carcinoma.

guished according to the predominant features (BELISARIO) but two or more may be combined in the same lesion

The *papulo-pearly* variety which is the commonest. The *cicatricial* variety most commonly found on the temporal and scalp regions. The *morphoea-like* variety The *button* variety The *cystic* variety in which small multiple translucent cysts contain a gelatinous fluid due to colloid degeneration. The *pigmented* variety which has to be differentiated from melanoblastomata in dark-coloured races particularly in the tropics where the latter are more commonly encountered The *cherry* variety which may also be transitional or wholly squamous in character The *rodent ulcer* slowly progressing over many years The *multiple superficial* variety which may be basal cell squamous cell metatypical in type is commonly intraepidermal but sometimes invades the dermis

*Atypical* lesions may be encountered in the form of localised lichenoid or eczematoid and crusted patches. The diagnosis in these can only be made



997 Pigmented basal cell carcinoma

998. Cystic basal cell carcinoma of the neck.

microscopically although chronicity and the presence of other typical lesions may suggest their character

*Areas of predilection* for basal cell carcinomata are the face more commonly above the mouth, the ears, neck, upper back and dorsa of the forearms and hands but other areas may be affected. Central ulceration, which may be covered by a crust, occurs eventually (the process may take years) Healing may take place with scar formation and periodical recurrence. Underlying structures may be involved such as bone or cartilage, followed by severe scarring

As a whole, basal cell carcinomata occur more commonly than squamous cell carcinomata although in some tropical areas *e g* Indonesia (Vos, TEN SELDAM) and in black-skinned races generally the reverse appears to be the case (HAZEN and FREEMAN). Any chronic nodular tumour or ulcer must be included in the differential diagnosis (see squamous cell carcinoma). Most basal cell carcinomata can be diagnosed clinically by the demonstration of the papulo-pearly nodules and rolled edge Where however any doubt exists a biopsy and microscopical examination should always be performed

*Clinical differentiating features from squamous cell carcinoma*

| *Basal cell carcinoma* | *Squamous cell carcinoma* |
|---|---|
| Slow growth | Fast growth |
| Late ulceration | Early ulceration |
| Papulo-pearly nodules and rolled edge | Absence of nodules and rolled edge |
| No tendency to metastasize | Tendency to metastasize |
| Telangiectasia more frequent. | Telangiectasia less frequent. |

*Rare cases of metastases have been reported from basal cell lesions* (BEADLES, FINNERUD, MACCORMAC, SAVATARD, SINGER etc.) *but some authorities, e.g.* WINER, *do not believe that metastases occur unless squamous cell changes, which may be atypical, have supervened.*

In dark races the presence of pigment may cause difficulty in differentiating basal cell carcinomata from malignant melanoblastomata.

## PATHOLOGY

The histology of basal cell carcinomata was first described by KROMPECHER (1900) though it is interesting to note that several of his cases seem not to have been what we now accept as such. KROMPECHER considered that basal cell carcinomata originated from the basal layer of the epidermis and for that reason attached the name to

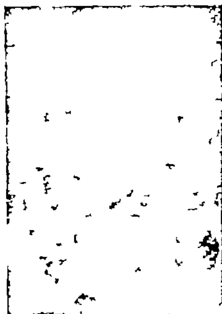


999 Morphea-like basal cell carcinoma.

this type of tumour. However, if we grant that the basal layer of the epidermis is the only one capable of dividing, this must also be the layer from which squamous cell carcinomata originate. Consequently this cannot satisfactorily explain the difference in histological picture between typical basal cell carcinoma and squamous cell carcinoma. Many theories have developed as to the true origin of basal cell carcinomata and it is widely accepted that they may originate also from the appendages of the skin (sweat glands, sebaceous glands, hair follicles). To stress this origin as much as HAWTHORN and FOOT have done and to call them all "*hair-matrix carcinomas*" (HAWTHORN) is in our opinion not justified. LENNOX and WELLS expressed their doubt whether [illegible] hair follicles exist and stressed the fact that in far more cases than is usually realised, fluid collections of some kind are found in the



1000 Slow growing basal cell carcinoma (30 years). Note supplementary blood supply



1001 Multiple superficial basal cell carcinoma.



100_ Perforating basal cell carcinoma.

growth, thus suggesting abortive sweat formation. They bring forward the hypothesis that basal cell carcinomata are the result of "a stimulus to proliferation normally supplied by the foetal dermis". From an extensive study of 850 cases THACKRAY concluded that the origin is from hair follicles, sweat glands or from the surface epithelium. Carcinomata of this histological type have never been experimentally reproduced so that the solution of the problem is still in doubt although we incline to the opinion of THACKRAY.

Fig. 1006 shows a basal cell carcinoma developing from a hair follicle. A multicentric origin is sometimes clear (see Fig. 1005) showing several small tumours as separate down growths close to each other.

It should be borne in mind that an area greater than that seen to be clinically affected might be predisposed to cancer formation. In this way it is possible to explain also the apparent development of squamous cell carcinoma in a basal cell tumour. We



1003. Cicatricial spreading basal cell carcinoma.

do not believe without further evidence that a squamous cell carcinoma arises from the cells of a basal cell tumour. We prefer to believe that the squamous cell tumour arises from the predisposed surrounding and intermingled epidermal cells skin and by its more rapid growth partly destroys the basal cell growth, giving the incorrect clinical impression that it originated from the basal cell tumour itself.

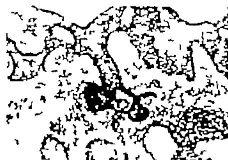
The histological picture of basal cell carcinoma is well known. The surface of the tumour is either centrally ulcerated or covered with a thinly stretched epidermis. In the more cystic types it may be well elevated above the surrounding skin surface. The tumour itself consists mostly of a solid central part with clubbed, rounded extensions into the dermis. The borderline between tumour and surrounding stroma is usually remarkably sharp. In some basal cell tumours cleft-like spaces are observed between the actual tumour and the surrounding stroma. Whether these are artefacts or actual collections of fluid is uncertain. The stroma often exhibits



1004 Basal cell carcinoma probably originating from hair-matrix.

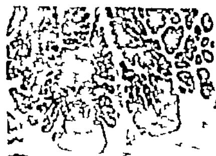


1005 Multicentric basal cell cancer



1006. Basal cell carcinoma
Development from abortive hair follicle





1007 1008 Basal cell carcinoma with clumps of melanin.

fibroels while so-called *Herxheimer spirals* can be seen with HEIDENHAIN haematoxylin (HAYTHORN). Sometimes special staining techniques (MALLORY phosphotungstic acid etc.) reveal a condensation of stroma around the growth resembling a basal membrane. The tumour cells are small and densely packed and have usually small, dark, slightly oval or rounded nuclei, very little cell-protoplasm and *no conspicuous nucleolus. The cell-borders are difficult to define, if at all. Cell-bridges* so-called "prickles" can only rarely be demonstrated. They are, however not always absent. The nuclei of the outer layers especially are usually slightly oval and can form palisades pointing to the centre of the tumour or its infiltrating projections. This is also true for the nuclei lining the smaller or larger cyst-like spaces that are found in a large percentage of basal-cell carcinomata. The nuclei may have a more flattened, endothelial-like appearance at these sites. In the central parts of the tumour the nuclei show no distinct pattern. The cells of the bulk of the tumour are usually remarkably similar. Mitotic figures are as a rule not difficult to find and sometimes are very numerous. Apart from definite cyst-like spaces,





1009 – 1010 Squamous cell carcinoma of the buttock.
*(Netherl. East Ind. Cancer Inst.)*

usually filled with lightly bluish tinged fluid in the normal haematoxylin and eosin stains some fluid can also be found at times more interspersed between strands of tumour cells, giving the appearance of spongiosa. Predominantly cystic tumours are sometimes encountered. Melanin may be present, and especially in dark-skinned races may be abundant, simulating the appearances of malignant melanoblastomata. In some tumours cornification is present and may appear in the form of whorls. These forms coincide with the "type mixte" of the "metatypical" group as described by DARIER. The basal cell tumours rarely if ever metastasize and only very few apparently authentic cases have been described in the literature (WILLIS).

The clinical behaviour of basal cell carcinomata can not be related to the histological type (LENNOX and WELLS, T... KRAY). There seems to be some indication that the extension, especially to the deeper parts of the dermis, has some prognostic bearing (TILA... KR... Y). The so-called *"type ... "* of the skin carcinomata can confidently be included amongst the basal cell carcinomata. Some doubt is indicated

about the "*type intermédiaire*" of DARIER, or transitional type. Every pathologist with experience of a large number of skin carcinomata will agree that occasionally one is seen which somehow cannot clearly be fitted into the group of the basal cell carcinomata or that of the squamous cell carcinomata. It might be anaplastic squamous cell carcinomata although this usually shows a different picture. These cases are really too rare, it seems, to justify a completely separate group. Their clinical behaviour is more malignant than that of basal cell carcinomata.

## SQUAMOUS CELL CARCINOMA

### *Symptomatology*

Lesions usually arise, either on clinically normal skin or supervening on a solar keratosis as hard opaque nodules with a verrucose or papillomatous surface but many commence as depressed, more or less flat, scale, erythematous indurations and infiltrations. In the tropics squamous cancer is quite frequently seen to originate from chronic ulceration. The growth possesses



1011–1012. Squamous cell carcinoma involving the bone.

a solid, infiltrated margin, ulcerates comparatively early usually when the diameter is between one and two centimetres, may be crusted, cornified or raw and granular with a tendency to bleed. Sometimes the lesions attain the appearance and size of a large cherry without ulceration. These *cherry-type* lesions have a relatively low grade malignancy and have been reported to involute spontaneously on occasion. Some have been reported under the heading of molluscum sebaceum MACCORMAC. FERGUSON SMITH described 2 cases for the first time (1934) under the heading of "*self-healing squamous epithelioma*". There appears to be a familial incidence and the histological picture is so similar to that seen in squamous cell carcinoma that microscopical diagnosis may not be possible (SOMMERVILLE and MILNE, SULZBERGER and BAER, CHARTERIS, WITTEN and ZAK).

Squamous cell carcinomata tend to become larger deeper modulated and ulcerated in the course of weeks. In the early stages, induration is localised and freely movable but later becomes diffuse somewhat depressed and

fixed. The growth may invade the underlying or upper tissues and the edges are always hard and everted. The ulcerated surface may be papillomatous or cauliflower like. This stage may be reached in a matter of months or not for two or three years and it is usually when the growth attains a size between two and three centimetres in diameter that glandular involvement becomes clinically evident. Septic contamination may possibly accelerate growth or dissemination of the tumour cells and may also account for local adenitis particularly with cancer of the lip.

Extension of a lesion into adjacent tissues may be rapid but metastases are not always frequent and more commonly occur from lesions on the hands and forearms than from lesions on the face except the lips.

*Areas of predilection* are the mucous membranes muco-cutaneous junctions, face, scalp ears neck, genitals and extremities particularly the backs of the hands although the feet and digits may also be affected. The lower extremities are more prone to be affected in natives in tropical areas (see Table I) Squamous cell lesions are much more commonly found than basal cell lesions on the lips, dorsa of the hands, feet and forearms (BELISARIO).

In general the greater the differentiation of a lesion and the less the invasive tendency the better is the prognosis Squamous cell tumours involving muco-cutaneous junctions tend to be more malignant than those involving the skin and less so than those on mucous membranes.

Diagnosis is best confirmed by biopsy and microscopical examination. A Wood's light filter in an ultraviolet ray lamp will produce fluorescence in ulcerated squamous cell lesions and only a deep violet appearance in other ulcers (RONCHESE)

## PATHOLOGY

In the precancerous state of squamous cell carcinoma the epidermis is usually thickened with hyperkeratoses and parakeratoses. The basal layer becomes irregular shows polymorphia and polychromasia of cells and nuclei extending into the ret Malpighi, sometimes most marked in the papillae. The corium shows extensive round-cell infiltrations mixed with plasma cells. As the growth develops, projections of the epidermis reach into the corium like the roots of a tree The central part quickly breaks down and the resulting ulcer may be covered with a crust of necrotic tissue mixed with lamellae of horn and sometimes also blood. The transition from normal to affected epidermis may be either abrupt or gradual. The infiltrating cords undermine the surrounding epidermis as well and this, in combination with the usually extensive inflammatory reaction, produces the raised edge that is clinically seen around the central ulceration. The demarcation of the epithelial downgrowths may be sharp but is usually less well-defined. A varying amount of anaplasia and mitotic figures are present. Cell-bridges can usually be detected in some places if carefully looked for In the central parts of the thicker cords, irregular cornification may take place to varying degree, which, on section, shows the typical "epithelial pearls" or whorls. On the other hand various degrees of anaplasia may be present even to the extent of giving a sarcomatous appearance (UND[illegible] *et al.*) Although the more anaplastic types usually will



1013. Ulcerated squamous cell carcinoma involving cartilage of the ear



1015. Squamous cell carcinoma.



1016. Squamous cell carcinoma of the lower lip



1014 Squamous cell carcinoma initially diagnosed as tropical ulcer

*(Netherl. East Ind. Cancer Inst.)*



1017 Squamous cell carcinoma involving the bone

exhibit more malignant behaviour It is doubtful if grading in various groups has much significance More reliance should be paid to such factors as the site and extension of the growth.

*Chronic ulcers of the lower limb*

Chronic ulcerations on the lower limb are of common occurrence in natives and in a certain percentage squamous cell changes are present. In many cases it is clinically impossible to diagnose or exclude malignancy with certainty and the pathologist is called in to decide the issue on biopsy material. It will be found that he, too, will often encounter difficulties that prevent him from giving a definite answer Successive stages of partial repair and renewed ulceration may lead to a distorted picture in which epithelial nests with cornification are alternated deeply in fibrous tissue. A few cases have been personally observed (TEN SELDAM) where the ulcer had extended into the tibial shaft and subsequent partial healing had led to the presence within the superficial bone of epithelial nests with cornification. It will be understood that the correct interpretation of such cases may be extremely difficult or impossible Even experienced pathologists will in some of these cases, not hesitate to diagnose a squamous cell carcinoma, but the subsequent clinical behaviour does not always warrant such diagnosis. Cases have been observed in which the patient had refused all forms of surgical treatment and developed no metastases, even after years, although the ulcer was still present, more or less unchanged

In treatment, too local removal, when possible, is generally preferred to mutilating amputations. For these reasons it seems advisable to be conservative in giving a microscopical report. The known behaviour of these ulcers indicates that true squamous cell changes are present far less often than is commonly thought

## METATYPICAL OR TRANSITIONAL CELL CARCINOMA

This group was divided by DARIER into the "*type mixte*" and the "*type intermédiaire*" As has been discussed under the section on pathology it is doubtful if such division is justified although occasionally cases are encountered which are difficult to fit in either the group of basal cell carcinomata or squamous cell carcinomata and which seem to respond generally less to radiotherapy than basal cell carcinomata. It seems doubtful if this justifies a separate grouping

## CUTANEOUS HORN

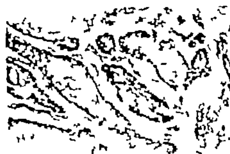
A cutaneous horn may arise from a sebaceous cyst filiform papilloma, verruca vulgaris naevus keratosis squamous cell carcinoma, clinically normal skin or mucous membrane. It consists of firmly welded lamellae of horn cells. Horns are usually single hard and may be short and stumpy or cylindrical long and pointed, twisted or angular They are yellowish to brownish black and may grow to several inches in length. A dermal collar usually surrounds the base which is subject to carcinomatous degeneration of the squamous type and should be treated accordingly Areas of predilection are the scalp forehead nose cheeks ears lips forearms hands and penis.



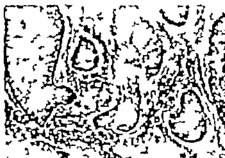
1018. Squamous cell carcinoma highly anaplastic growth.



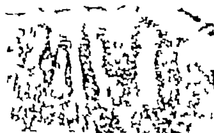
1019 Squamous cell carcinoma less anaplastic type some indication of cornification present.



1020 Squamous cell carcinoma More differentiation formation of "pearls"



1021 Squamous cell carcinoma highly differentiated type resembling pseudo-epitheliomatous hyperplasia.





1022 1023 Squamous cell carcinoma in solar keratosis. Growth still intra-epidermal. Note differentiation of basal and rete cells.



1024 Cutaneous horn.

### PATHOLOGY

The central part shows an excessive hyper and parakeratosis. The underlying epidermis is only a few layers thick but the cells of the basal layer and the connecting cells of the rete Malpighi show some irregularity and occasional mitotic figures. The papillae are flattened, gi ing "stretched" appearance of this central part. Around the deeper central part, a wall of thick epidermis is found with marked acanthosis and sometimes dyskeratosis as well. This "wall" usually passes quickly into normal epidermis. The corium contains a variable but commonly considerable number of lymphocytes and plasma cells.

## INTRA-EPIDERMAL AND SUPERFICIAL CARCINOMATOUS CONDITIONS

Certain neoplastic growths with a considerably rarer incidence than the foregoing lesions may remain confined to the epidermis for many years before further malignant changes become clinically evident. These comprise Bowen's disease, Queyrat's erythroplasia, Paget's disease and multiple superficial basal cell carcinomata. All have certain common features and combined forms may occur (MATSUMOTO)

### BOWEN'S DISEASE

This condition is an intra-epidermal carcinoma and can closely resemble Queyrat's erythroplasia or Paget's disease. Lesions appear as sharply defined, papulo-squamous plaques which may be single or multiple with normal or slightly erythematous surrounding skin. They may be dark red or brown in colour with a fine scaly surface and the centre may be retracted. Other plaques may be covered with thin yellow gray brown or black crusts

under which is a flat, red, papillary sometimes oozing base. In some cases atrophy may make the appearance more macular than papular. Peripheral extension occurs without induration.

The lesions occur mainly on the trunk but may occur elsewhere including the mucous membranes where they exhibit a slightly thickened red, velvety appearance which may be masked by areas of leucoplakia.

Clinical malignancy (squamous cell changes) is manifested by a nodule or nodules which may fungate or ulcerate, and metastases which are rare, may occur before there is clinical evidence of malignancy in the primary lesion. Metastases may occur from true Bowen's carcinoma or the development of an atypical epidermoid carcinoma (ANDREWS). The condition should be



1025 Bowen's disease.

differentiated by biopsy from the following: seborrhoeic keratosis, solar keratosis, industrial keratosis, arsenical keratosis, leucoplakia, lupus erythematosus, lichen Vidal, tinea circinata, Paget's disease, Queyrat's erythroplasia, chronic patches of eczematitis, psoriasis, multiple superficial basal or squamous cell carcinomata.

## QUEYRAT'S ERYTHROPLASIA

The lesions may be single or multiple, rather firm, sharply defined maculopapular, usually slightly erythematous patches of various sizes on the glans penis, prepuce, vulva, lips, tongue, buccal mucosa and muco-cutaneous junctions. The surface of the lesion is dry, smooth, shiny and red with a somewhat velvety appearance. There may be irritation or oozing but rarely scaling or crusting. Should ulceration or papillomatous growth supervene, which is the usual course of events in the long run, they denote the devel

opment of squamous cell changes. Metastases have been observed in regional lymph glands from clinically unchanged lesions. The diagnosis (by biopsy) has to be made from lichen planus, lichen Vidal, psoriasis, leucoplakia, lichen sclerosus et atrophicus, kraurosis, lupus vulgaris, lupus erythematosus (in the mouth region) and the superficial carcinomata.



1026. Bowen's disease. Intradermal carcinoma with "halo cells"

*(Inglis–Sydney)*

## PATHOLOGY

Both conditions are essentially intra-epidermal squamous cell carcinomata. Their differentiation lies more in the clinical aspect and usual localisation than in any definite difference in histology. In both lesions the epidermis or mucous membrane affected is much thickened with coarsening or disappearance of the papillae. The papillae may become broad and blunt. The cells and nuclei of the epidermis, especially in the stratum spinosum, are irregular in size and shape. Mitotic figures are present. Especially in Bowen's disease large, sometimes multinucleated, cells are found with hyperchromatic nuclei in the centre surrounded by a clear halo (see Fig. 1026). Some hyperkeratosis and parakeratosis is found over the affected area.

The corium shows considerable inflammatory reaction.

## PAGET'S DISEASE

### *Symptomatology*

Paget's disease of the breast is a carcinoma from the beginning (MACKIE and CIPOLLARO) which commences in one or more lactiferous ducts near their

outlets and extends intra-epithelially down the ducts and also upwards to form an intra-epidermal carcinoma (INGLIS).

Extra-mammary Paget's disease appears from the evidence available to occur in the areas of the lacteal lines and other regions of the body where apocrine glands are found.

The condition usually occurs on the breast in women but may occur in men. It appears as a red, scaly sometimes irritable patch which extends slowly with a well-defined and sometimes papular edge. The surface is usually covered with crusts and scales removal of which reveals red eroded or oozing areas and white, macerated islands of epidermis. Some fissuring may be present and the nipple may appear normal thickened, retracted or destroyed. The disease may involve the whole breast or spread



1027 Paget's disease. Paget cells in the epidermis.

to the trunk. The lesions may be tender and accompanied by itching burning or pain from friction of clothing The condition is unilateral and may be preceded by a serous or blood-stained discharge from the nipple. It is progressive and not characterized by remissions. A tumour in the breast may appear early or not for some years and is followed eventually by glandular involvement and systemic metastases. The former may precede a palpable breast tumour Extra-mammary manifestations are usually single red, sharply defined, eczematoid patches varying in size up to an inch or more in diameter Lesions may be scaly and dry or exudative eroded and crusted. Multiple lesions and lesions containing one or more nodules are occasionally seen.

## PATHOLOGY

Paget's disease is characterised by the presence in the epidermis of large clear "Paget cells" with relatively large nucleus containing at least one conspicuous nucleolus (see Fig 1027). An intraductal carcinoma of variable size and extension is always present in the affected breast. It is held that this intraductal carcinoma is due to the spread of a Bowen-like disease of the skin into the ducts and that the usually co-existent breast carcinoma is unrelated to the Paget condition (WILLIS). On the other hand it is widely accepted that an intraductal carcinoma is the primary cause of the condition, spreading into the surrounding epidermis. We are in agreement with this concept. Apart from the convincing evidence brought forward by INGLIS, it would be most peculiar that the ultimate growth is never squamous cell carcinoma, which is always the type of tumour that develops from Bowen's disease.

Paget's disease must be differentiated principally from lichenoid dermatitis or eczematitis which occur at any age, exhibit no induration or nipple deformity and respond to treatment. ANDREWS has observed a case in which a localised dermatitis cleared up and recurred on several occasions before Paget's disease developed. Other conditions to be differentiated are psoriasis verrucae, lupus erythematosus superficial carcinomata and Bowen's disease. In the performance of a biopsy for diagnosis when a lesion is around the nipple, a portion of the nipple should be included.

## MULTIPLE SUPERFICIAL BASAL CELL CARCINOMA

### *Symptomatology*

These lesions which may be single, commonly appear as multiple nummular or oval areas and commence with pinhead-sized pink or yellowish brown spots mainly on the trunk. They extend peripherally or enlarge by coalescence to form flat sharply demarcated, rounded or creeping patches sometimes containing papules. Stretching of the lesions will reveal in most cases a thin, thread-like papulo-pearly edge which is sometimes slightly elevated. On occasions there is partial central healing with superficial atrophic scar formation with or without telangiectases. Subjective sensations are slight or absent. The differential diagnosis is similar to that for Bowen's disease. The diagnosis is confirmed by biopsy

## THERAPY

### *Basal and Squamous Cell Carcinomata*

The erroneous impression that more radiation is required to cure most squamous cell carcinomata than basal cell carcinomata has arisen from lack of appreciation of the greater degree of depth of penetration of the former. Failure to take this into consideration in estimating the dose to the base of a squamous cell lesion with consequent failure to cure has created this illusion.

For early carcinomata the following routines are recommended

*X-rays*

(Factors employd 80 to 110 K.V P., 20 cm. F.S.D 4 to 6 M.A., 1 2 mm. Aluminium H.V.L.)

1 *Single dose techniques*

These techniques should be employed preferably when a patient is unable to attend for treatment more than once

) The presenting growth is removed with a cautery or diathermy followed by curettage and residual bleeding is stopped by further light cauterization. This is followed immediately by a dose of 1800 r to the base of the treated area including from 0.5 to 1 0 cm of surrounding tissue.

*b*) If X-rays alone are employed, a dose of 2500 r (occasionally 3000 r If much thickening is present) is delivered, two thirds to an area 0.5 to 1 0 cm wide of the lesion and one third shielded almost up to the visible or palpable edge By using two areas of different sizes, the depressed appearance that sometimes follows large dose delivered to a single area, particularly on the face is minimized or avoided. The diameter of the treated area should not exceed 3.5 cm in either case.

2. *Short fractionation techniques*

) For small early superficial lesions three doses of 1000 are delivered on three consecutive days (total dose 3000 r"), again varying the size of the screen aperture daily from 1.0 cm wide of the lesion to a slightly smaller one each day to minimize possible later depression of tissue.

*b*) For later deeper and more indurated lesions, fiv doses of 800 r are de livered daily for fi consecutive days (total dose 4000 r"). The diameter of the areas treated should not exceed 3.5 cm in the former case and 5 cm in the latter and should include 1.0 cm of clinically normal surrounding tissue.

3 *Long fractionation techniques*

Selection of these techniques is based on the following considerations Firstly areas like the dorsa of the hands and feet or the temporal region do not heal so readily as other areas (*e g* the cheeks) after radiation, owing to a poorer blood supply Also covered surfaces of the body tend to develop telangiectases more than exposed areas.

Secondly the larger the area treated, the greater the tissue damage from backscatter (allowance for which must be made in computing dosage) and the greater the tissue injury effect, a phenomenon separate from backscatter which also delays and disturbs healing (BELISARIO).

Thirdly the cosmetic effect in general (within therapeutic limits) is improved in proportion to the greater fractionation of the dose of radiation.

) For smaller lesions not on areas which heal less readily a total dose of 3500 is delivered in ten days in seven increments of 500

*b*) For larger lesions, and those on areas of poorer healing capacity such as the dorsa of the hands and feet, a total dose of 4500 is delivered o fifteen increments of 300 r over three weeks.

Based on my own experience o er twenty five years, and that of the majority of dermatologists in Australia, where the incidence of cutaneous carcinomata is

## PATHOLOGY

Paget's disease is characterised by the presence in the epidermis of large clear "Paget cells" with relatively large nucleus containing at least one conspicuous nucleolus (see Fig. 1027). An intraductal carcinoma of variable size and extension is always present in the affected breast. It is held that this intraductal carcinoma is due to the spread of a Bowen-like disease of the skin into the ducts and that the usually co-existent breast carcinoma is unrelated to the Paget condition (WILLIS). On the other hand it is widely accepted that an intraductal carcinoma is the primary cause of the condition, spreading into the surrounding epidermis. We are in agreement with this concept. Apart from the convincing evidence brought forward by INGLIS, it would be most peculiar that the ultimate growth is never a squamous cell carcinoma, which is always the type of tumour that develops from Bowen's disease.

Paget's disease must be differentiated principally from lichenoid dermatitis or eczematitis which occur at any age, exhibit no induration or nipple deformity and respond to treatment. ANDREWS has observed a case in which a localised dermatitis cleared up and recurred on several occasions before Paget's disease developed. Other conditions to be differentiated are psoriasis, verrucae, lupus erythematosus, superficial carcinomata and Bowen's disease. In the performance of a biopsy for diagnosis when a lesion is around the nipple, a portion of the nipple should be included.

## MULTIPLE SUPERFICIAL BASAL CELL CARCINOMA

### *Symptomatology*

These lesions which may be single, commonly appear as multiple nummular or oval areas and commence with pinhead-sized, pink or yellowish brown spots mainly on the trunk. They extend peripherally or enlarge by coalescence to form flat, sharply demarcated, rounded or creeping patches sometimes containing papules. Stretching of the lesions will reveal in most cases a thin, thread-like, papulo-pearly edge which is sometimes slightly elevated. On occasions there is partial central healing with superficial atrophic scar formation with or without telangiectases. Subjective sensations are slight or absent. The differential diagnosis is similar to that for Bowen's disease. The diagnosis is confirmed by biopsy.

## THERAPY

### *Basal and Squamous Cell Carcinomata*

The erroneous impression that more radiation is required to cure most squamous cell carcinomata than basal cell carcinomata has arisen from lack of appreciation of the greater degree of depth of penetration of the former. Failure to take this into consideration in estimating the dose to the base of a squamous cell lesion with consequent failure to cure has created this illusion.

For early carcinomata the following routines are recommended

The tumour is then treated in the ordinary way and there is no risk of later radiation cataract as in the case of radium.

*Ears and nose*

Fractionation should be employed in these situations since this produces less interference with the blood supply over cartilage and subsequent healing. The cross-fire method can be employed and the cosmetic effect is far superior to that obtained by surgical procedures, to which resort can still be made in the rare event of failure.

*Radium*

*Radium plaques* may be employed for early lesions but an even distribution of dosage is difficult to obtain and the depth dose is inadequate owing to the inverse square law.

*Radium or radon needles* are to be preferred. The technique recommended is that devised by PATERSON and PARKER.

Platinum needles with a filtration of 0.8 mm are arranged on a mould at a distance of 0.5 to 1.0 cm so as to give an even distribution of dosage (6000 r) over a period of eight days. For the dorsa of the hands and feet, the time of application is best extended to fourteen days.

Interstitial radiation can also be employed but is liable to be followed by necrosis over areas where there is a dearth of overlying soft tissue and the blood supply is poor, e.g. the backs of the hands, the ears or nose.

The use of radon seeds is often followed by foreign body reactions, necrosis or both.

*Contact X-ray Therapy*

Some workers prefer this method originally described by CHAOUL and employ dosages ranging from 1500 r to 15000 r at from 30 to 60 kilovolts. Dosages most commonly employed range between 4000 r and 8000 r in daily increments of 300 r to 600 r or 1000 r every second day.

The Chaoul contact therapy apparatus has a half value layer approximating 3.3 mm of aluminium, whereas the tube of the more recently employed Philips apparatus has an inherent filtration of only 0.2 mm of aluminium, thus emitting much softer radiation.

The disadvantages attending this form of treatment are the limitation of depth dose due mainly to short focal skin distance and the limited area (approximately 2.5 cm in diameter) which can be treated in one application of radiation. Contact therapy is, however, quite efficient for small superficial lesions.

*Fast Electron Therapy*

Boor has employed electrons with maximum energy of 6 M.V. corresponding to a range of 3.0 cm. At two thirds of the range of the electrons, the depth dose is 100 per cent of the surface dose, after which it rapidly falls to zero. Thus the deeper as well as the superficial structures are considerably spared allowing greater

safety than X rays or radium in the treatment of subcutaneous metastases as well as surface tumours.

*Radioactive Isotopes*

Radioactive isotopes provide further sources of radiation than those in use at present. Their therapeutic possibilities are being investigated. They are being used for the treatment of cancers which may have an affinity for the parent element, e g the isotopes of iodine [131]I and [131]I. It is necessary that their breaking down period should not be too long or their radioactivity may be carcinogenic rather than curative (OLIPHANT). Isotopes that emit gamma rays include cobalt 60, europium 154 and 152, and caesium 134 and 137 Substances emitting almost pure beta radiations include yttrium 90 (through its parent strontium 90), rhodium 106 (ruthenium 106) promethium 147 praseodymium 144 (cerium 144), and phosphorus 32 (EDDY) So far therapeutic results have been no better than those obtained by conventional radiation methods.

*Cautery*

A cautery especially a post cautery is the treatment preferred by some dermatologists (SUTTON JR, JACOBSON and ALCON). It is of particular value in combination with X-radiation or carbon dioxide snow or in the removal of a recurrent lesion when further radiation is inadvisable. When used alone on large lesions, the treated area, which should include 0.5 to 1 0 cm of tissue wide of the growth, should be massaged daily to produce a supple scar

*Electrodesiccation and Electrocoagulation*

Monopolar or bipolar currents may be employed to utilise a desiccation spark, electrocoagulation or the actual cutting knife under the same circumstances as a cautery

*Scalpel Surgery*

In some cases scalpel surgery is the method of choice e g on the scalp where loss of hair would follow radiation, or on the back of the hand in a manual worker since a knock on a healed irradiated area may cause an ulcer in the devitalised tissues. It is also of value particularly plastic surgery for recurrent lesions in previously irradiated areas. The possibility of keloid formation can be lessened if not removed by the instillation of a solution of compound F into the would before suturing (ARNOLD JR) Scalpel surgery is the method of choice either alone or combined with radiation, for the large squamous cell lesions and glandular involvement found on the lower extremities of natives in tropical areas. This also applies to glandular involvement in general BODE s fast electron therapy may however prove useful in this respect.

*Carbon Dioxide Snow*

For superficial lesions such as multiple superficial basal cell carcinomata and Bowen s disease carbon dioxide snow is the treatment of choice both for

cosmetic reasons and its ease of application to multiple lesions (B). CARO and others are of the same opinion.

It may be employed as the solid stick (which can be moulded against a hot tap or water pipe to the size of the area to be treated) or combined with acetone to form a slush and applied on the end of a wooden probe tipped with cotton wool. The time of application varies from 20 to 60 seconds depending on the thickness of the lesion to be treated. When nodules are present, the prior removal of these with a cautery followed by carbon dioxide slush will still produce better cosmetic results than other forms of treatment without the possibility of later telangiectases following irradiation. The slush is preferable to the solid stick as no pressure is required with the former so that bulla formation and delay in healing are lessened. Liquid nitrogen or oxygen may be employed but are less convenient and have no advantages over carbon dioxide slush.

*Chemosurgery*

Destruction of surface tissue with dichloracetic acid followed by the application of a zinc chloride fixative and a water-tight dressing has been employed by MOHS. Each day 1.5 mm of tissue is removed with a scalpel, cut into sections and examined microscopically. The procedure is continued until all cancerous tissue has been removed. ALLINGTON and associates have also employed this modality with success. It is however somewhat more tedious than other forms of therapy.

*Ultrasonic Radiation*

Ultrasonic radiations have not so far proved useful therapeutically for carcinomata since their destructive action on carcinomatous tissues is too closely approximated by that on normal tissues.

*Adjuncts to Present Forms of Therapy*

These procedures enumerated below have produced deleterious effects on carcinomatous cells and some have produced complete involution of lesions.

1. Injection of splenic and liver extracts into carcinomatous lesions (AMERSBACH *et al.*; effective in the hands of one of us in a proportion of cases (B)).

2. Local applications of podophyllin varying from 15 per cent. to 30 per cent. in strength at daily or longer intervals, sometimes preceded by curettage (SMITH and GARRETT; WALSH-C[illegible]).

3. Bi-weekly applications of colchicine 0.5 to 1.0 per cent. and bulbocapnine 0.5 parts in vaseline 30 parts followed by an alcoholic solution of 0.05 parts of colchicine in 5 millilitres of alcohol and saturated solution of bulbocapnine in 50 per cent. alcohol (HIRSCH).

4. The prior production of erythema by infra-red or ultra-violet rays lessens the amount of X-radiation required for a given therapeutic effect, possibly due to increased oxygenation in the area in question (BELLIS and ELLIS).

5. Intra-venous vitamin K (which has an inhibitory effect on mitosis) in conjunction with X-radiation (ELLIS). It has not proved effective as a local injection in the hands of one of us either alone or in conjunction with irradiation (B).

6. Hormones internally or injected locally alone or in conjunction with radiotherapy.

7. Nitrogen mustard administered orally.

8. Parenteral injection of material obtained from a serologically active lipoid from the liver of cancer-bearing patients, cancerous tissue or both. This lipoid has been used with a high degree of reliability as a test for internal cancer based on an underlying specific immunological reaction (PENN and JACOBSEN, PENN HALL *et al.*)

### *Paget's disease*

Surgery alone or in conjunction with radiation is the method of election. The extra mammary type is treated like Bowen's disease. This also applies to Queyrat's erythroplasia in the early stages or Sach's lotion (neoarsphenamine 0.3 g dissolved in 4 ml of distilled water and 1 ml of glycerine) may be applied twice weekly. In the later stages resort must be had to surgery with or without radiation.

## PROPHYLAXIS

This consists of avoiding over-exposure to the sun and the early removal of pre-carcinomatous lesions or small tumours in areas subjected to any form of trauma. Broad brimmed hats, loose covering clothes and sun-ray repellent applications containing such substances as menthyl salicylate 2 per cent, quinine tannate 4 per cent, or paraaminobenzoic acid 15 per cent may be employed. It is important that these substances should be incorporated in the outer phase of an emulsion (POLLARD). Injections of crude liver extract may help (ANDREWS).

## PROGNOSIS

The prognosis in early *basal cell carcinomata* is good. In later or inadequately treated cases it depends on the extent of infiltration (THACKRAY) and adjacent tissue involvement and whether squamous cell changes have occurred. Gradation in behaviour depends on the degree but not on the type of differentiation of the cells in a growth (LENNOX and WELLS). Pigmented basal cell lesions have never metastasized (LENNOX).

The prognosis in *squamous cell carcinomata* is mostly good in early cases. In general it depends on the location (e.g. metastases are more frequent from the lips and lower parts of the extremities), duration, age, degree of anaplasia, radiosensitivity and the occurrence of metastases. In the latter case it is usually bad, also in the more anaplastic lesions.

*Cutaneous horn* has a good prognosis in general unless untreated, when it depends on whether squamous cell changes have taken place at the base.

*Bowen's disease* and *multiple superficial basal cell carcinomata* may remain unchanged for many years. The prognosis on the whole is good but depends on the efficiency of treatment and whether or not malignant changes have occurred.

*Queyrat's erythroplasia* may also remain stationary for years, but a metastasizing carcinoma usually develops eventually and the prognosis deteriorates accordingly.

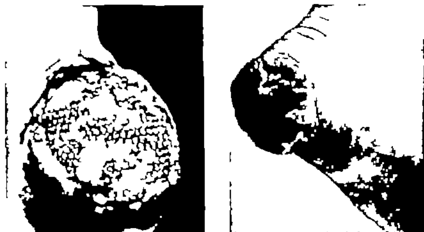
*Paget's disease* of the breast should always have a guarded prognosis although permanent cure usually follows early diagnosis and efficient treatment before metastases have occurred. The prognosis in the extra mammary type is similar to that of Bowen's disease.

# MALIGNANT TUMOURS OF DOUBTFUL ORIGIN

## MALIGNANT MELANOBLASTOMA

The term malignant melanoblastoma is preferable to the other synonyms since these tumours arise from melanoblasts in which pigment is absent. Thus, contradictory terms such as non-pigmented melanocarcinoma are avoided. Also the term melanoma alone simply denotes a pigmented tumour whether malignant or benign.

It is well to realise that primary malignant melanoblastoma is not only



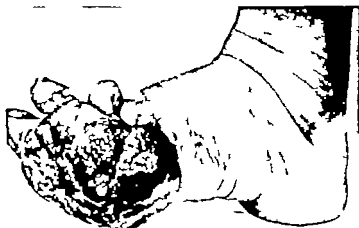
1028 – 1029 Malignant melanoblastoma of the heel.

observed in the skin. The next most frequent localisation is the eyeball though it is interesting to note that amongst Indonesians no primary melanoblastoma of the eyeball was never observed (MULOCK HOUWER, SOETIDJO HARDJOSOE-KATMO). Occasionally they find their origin in the mucous membranes of nose mouth and rectum. It is extremely dubious if so-called primary malignant melanoblastoma of internal organs (liver adrenals leptomeninges) really can be looked upon as being of primary origin. It is quite possible that a

Syn. Melanoma, Malignant Melanoma, Melanocarcinoma, Naevocarcinoma, Naevomelanoma, Melanosarcoma.

small primary lesion has been removed from the skin many years before with the diagnosis of a benign mole or the primary lesion may not even be discovered and the patient or his family (when the diagnosis, as may happen, is only made post mortem) has forgotten all about this.

It is still sometimes thought that malignant melanoblastoma is rare





1030–1031 Malignant melanoblastoma.
*(Netherl. East Ind. Cancer Inst.)*

amongst dark-skinned races. From observations in America (MORRIS and HORN) we learn that amongst the white population malignant melanoblastoma is from 1.8 to 4.4 times as frequent as amongst the Negro population.

In relation to the absence amongst Indonesians of these tumours originating in the eyeball it is interesting to note that in the statistics of MORRIS and HORN about Negroes 28 cases of this condition were observed in a total of 430. Observations from elsewhere (VOS, BISHOP BONNE, HEWER SOETIDJO HARDJOSOEKATMO, TEN SELDAM) indicate that *in more primitive living dark-skinned races especially those whose peoples commonly go barefooted, malignant melanoblastoma is far from rare*.



1032–1033 Malignant melanoblastoma originating in or as a naevus.

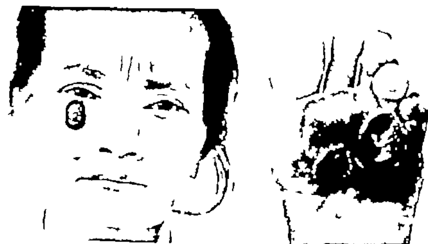
TABLE IV

MALIGNANT MELANOBLASTOMA

| Localisation | WAMINK (Holland) | E. J. MACDONALD (U.S.A.) | Dutch East Indian Cancer Institute: VOS | Dutch East Indian Cancer Institute: S. HARDJOSOEKATMO | Dutch East Indian Cancer Institute: TEN SELDAM |
|---|---|---|---|---|---|
| Eye | ? | 65 = 18½ | — | — | — |
| Head and neck | 8 | 65 | 5 | 10 | 22 |
| Body | 8 | 65 | 2 | 4 | 5 |
| Arms | 2 | 41 | 2 | 5 | 5 |
| Thighs | 2 | | 3 | 6 | 6 |
| Lower legs | 3 | } 74 = 21.2 | 3 | 6 | 10 |
| Sole of feet | 4 } | | 44 } | 73 } | 85 } |
| Toes | 1 } 22.5 | | 8 } 82.5 % | 12 } 72 % | 14 } 68.3 % |
| Rest of feet | 2 } | | 14 } | 33 } | 41 } |
| Rest of body | 1 | 39 | 2 | 15 | 17 |
| Total | 31 | 349 | 83 | 164 | 205 |

It might well be that the custom of going barefooted, and so exposing the feet to all kinds of traumata, has some connection with the high incidence of these tumours on the toes and feet of the dark skinned races. The difference from the statistics in white people is striking (see Table IV). It is very difficult, almost impossible, however, to estimate the absolute frequency of these lesions and their relative importance in relation to malignancies of other organs. It can only be stated that they are far from rare in dark skinned races. It would appear significant that the 205 malignant melanoblastomata mentioned in Table IV were observed in the same time period as the 893 skin carcinomata in Table I.

Malignant melanoblastomata arise in moles (soft naevi) in approximately



1034–1035 Malignant melanoblastoma.
*(Netherl. East Ind. Cancer Inst.)*

25 per cent of cases. They usually arise in normal skin in the form of lentigo maligna (BECKER, MIESCHER).

BECKER and McGOVERN believe that the malignant cells have their origin in normal melanoblasts at the epidermo-dermal junction rather than in the naevus cells themselves. S[illegible] considers that naevus cells (*fully formed*) can become malignant. MEIROWSKY and FREEMAN suggest that filtrable melanin granules may represent the carrier or [illegible] agent. They also put forward evidence that nuclei, nucleoli or nuclear derivatives of connective tissue cells can produce melanin autochthonously and therefore may give rise to melanosarcomata.

Intra-epidermal and [illegible]radermal naevi do not become malignant (TRAUB, SACHS *et al.*, M[illegible] [illegible] T[illegible] SELD[illegible] *et al.*). It is the junctional type where mature nae[illegible] [illegible] as well as clear cell melanoblasts are distributed in the

basal layer of the epidermis and the adjacent layers of the epidermis and dermis and for this reason the majority of lentigines are not considered to be junction naevi (WINER, SACHS). The more potentially dangerous soft naevi or moles are the dark brown, blackish, slaty or gunmetal coloured types, usually less than two centimetres in diameter.

BECKER and OBERMAYER have stated that since melanoblasts have been shown to arise independently from and wander secondarily to the epidermis, the malignant tumours "melanomata" cannot be considered to be of epidermal origin and should be designated as sarcomata and not carcinomata.

MASSON stated that simple pigmented areas (junctional naevi) are malformations produced by functional overactivity of the melanoblasts in the epidermal basal layer accompanied by an over-proliferation of melanoblasts or by a localized over activity in melanogenic function possessed by these melanoblasts. Also the precise origin of melanoblasts whether from the epidermis or neural crest, is still obscure.

Moles have two origins (a) from proliferation of intra-epidermal melanoblasts followed by downward migration into the dermis and (b) from the proliferation of the Schwannian cells of dermal nerves with subsequent migration upward into



1036. Melanoma at the back of the ear
(Fazel-San Francisco)

the dermis. Fusion of the two forms the naevoid tissue. While there is migration of melanoblasts naevus is compound, when this ceases it has become intradermal.

The fact that naevus cells are radio-resistant is suggestive evidence of their neural origin (B).

FITZPATRICK has shown that the cells of malignant melanoblastomata possess a positive tyrosinase reaction.

BECKER Jr. *et al.* state that the tyrosinase reaction may be associated with the malignant character of human pigment cells (melanodendrocytes) and this reaction may provide a new approach to the diagnosis of malignancy in pigmented neoplasms and to the differentiation of amelanotic malignant melanoblastomata from such lesions as fibrosarcoma and squamous cells carcinoma. MONTGOMERY now

agrees with BECKER and OBERMAYER that the clear cells of MASSON are identical with the pigment forming dendritic cells, pigment is not formed by the basal cells as formerly thought, and the Langerhans cell is a dendritic celle at the epidermo-dermal junction

It is possible a hereditary factor may be concerned in these malignant growths (COWLEY). Hormonal influences may also play a part since these lesions rarely spread or metastasize before puberty despite suggestive microscopical appearances (SCHARNAGEL and PACK, WEIDMAN).

During pregnancy benign melanoblastomata may become malignant, though such might be due to metabolic influences without any direct hormonal influence on the tumours. But estimations of the intermedin content of the serum of patients with malignant melanoblastomata are suggestive of a relationship between this hormone and the malignancy (GESCHICKTER TEN SELDAM). The Pussy melanomas of mice are stimulated to increased growth by repeated injections of intermedin (SUGIURA). That hormonal influences, especially from testosterone play a part in the pigmentation of the skin is well-known. In eunuchs there is always an almost pathognomonic paleness and peculiar tinge of the skin with little or no tendency to pigment formation when exposed to U V rays or sunlight.

It is well to remember that hormones play an important part in the pigmentation of lower animals (bridal colors in fish mating colors in birds).

What influence hormones play in the development of malignant melanoblastomata is still unkown.

Chronic irritation or frequent trauma may on occasion be the trigger mechanism for the initiation of malignant changes. Particularly is this so in the tropics where the incidence of malignant melanoblastomata is higher among natives and most lesions originate on the soles or legs where injury is common (TEN SELDAM). HEROLD VINT If this is so penetrating civilization should eventually lower the incidence of these tumors.

There is no conclusive evidence that a single injury e g a biopsy has ever initiated malignancy in a mole (B).

## SYMPTOMATOLOGY

Melanoblastomata may arise in apparently normal skin in addition to lentigines and moles They are rare in hairy moles and it is doubtful if they ever arise from blue naevi or Mongolian spots. Areas of predilection are the lower extremities but they may occur on other sites. They never occur in the eyes in Indonesia (MULOCK HOUWER)

If the lesions arise on clinically normal skin, the first sign may be a small brown or black spot followed by rapid growth infiltration and ulceration. Marked pigmentation when present is suggestive of the diagnosis. Fine lines of pigment may extend along the lymphatics indicating dissemination. Inadequate treatment is followed by rapid recurrence in the form of raised multiple, metastatic, satellite nodules round the original focus.

The clinical signs of commencing or present malignancy in a mole are:

1 Increase in size 2. Increase in depth and extent of pigmentation 3. Crust formation 4 Inflammatory areola 5 Bleeding 6. Ulceration 7 Nodules in or around the lesion 8 Regional adenitis.

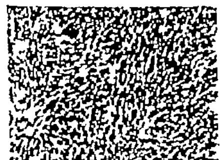
## MALIGNANT MELANOBLASTOMA



1037 Highly pleomorphic resembling rhabdomyosarcoma.



1038. Nerve-like structure.



1039 Resembling fusicellular sarcoma.



1040 Resembling mixed cell sarcoma.



1041 Secondary in lymphnode resembling carcinoma.



1042. Carcinomatous type.

*Metastases* usually but not invariably appear in the neighbouring lymph glands before the internal organs They may exhibit an increase or decrease in pigment compared to the primary lesion and show wide variations in cell types. At times generalized pigmentation takes place and melanuria may occur

Of the internal organs the liver and lungs are most frequently invaded. The primary lesion may be present a long time without visible metastases and also may be insignificant compared with their extent.

*The melanotic "whitlow" of* HUTCHINSON is characterized by paronychia surrounded by streaks or nodules of neoplastic tissue A fungating ulcerating



1045 Malignant melanoblastoma.

tumour soon develops followed by dissemination *Pigmented naevi under or at the edges of the nails between the digits or on the palms and soles are usually more potentially dangerous* Sometimes they are so small as to escape detection even after metastases have occurred. The differential diagnosis is similar to that for squamous cell carcinomata with the addition of dark haemangiomata, angiofibromata haemangioendotheliomata and dark tattoo marks. Sometimes a contusion round such lesions as a plantar wart may be temporarily suggestive Confirmation by biopsy and microscopical examination should be made in all cases

In the case of a suspected pigmented naevus there is no risk of initiating

or increasing malignancy and dissemination by the performance of a biopsy provided a report is obtained within 48 hours and excision performed then if necessary (TRAUB, SACHS *et al.*, BECKER, WINER, WEIDMAN, MONTGOMERY, MCGOVERN, BELLISARIO *et al.*). On general principles it is wise in the performance of a biopsy to remove small lesions as a whole with a view to obtaining the best cosmetic effect.



1044. Malignant melanoblastoma of the eye-lid.
*(Netherl. East Ind. Cancer Inst.)*

## PATHOLOGY

It is widely accepted that malignant melanoblastomas of the skin arises either from normal skin or from junctional naevi, never from intradermal naevi. This view seems to be too dogmatic in the opinion of one of us (t.S.). The rapid growth of malignant melanoblastomata often makes it impossible to decide where they arise.

So-called *juvenile melanoma* is sometimes met with in children before puberty. Their seemingly malignant histological characteristics are usually *not* confirmed by their clinical behaviour. It is wrong, however, to hold that they are never malignant (PACK, MCGOVERN). One of us (t.S.) has observed a case of malignant melanoblastoma originating from a naevus on the back of an Indonesian

boy not older than eight. He died with widespread metastases within six months of detection of the primary lesion.

It seems to be purely academic to argue whether malignant melanoblastomata originate only from the "clear cells" in the epidermis (BECKER) or also from naevus cells. The question really is, can naevus cells become malignant? Since benign naevi may contain mitotic figures, it would be indeed strange if malignant changes could not take place in them.

Even the most malignant tumours tend to grow in an expansile rather than in an infiltrating manner

The histology of malignant melanoblastomata is characteristically variable Appearances resembling sarcoma and carcinoma are both encountered. Sometimes a nerve like arrangement is seen (see Fig 1038). Some growths show enormous variety in size and shape of nuclei and cells as well as in tinctorial reactions. Giant



1045 Myosarcoma of the knee.
(*Netherl East Ind. Cancer Inst*)

cells of various forms with several nuclei may be present. If in such growths melanin is absent the distinction from rhabdomyosarcoma may be extremely difficult or impossible. Mitotic figures are common. Melanin in various amounts is usually present. Melanin in the tumour cells is usually fine and dust-like. Extra cell lar melanin in larger masses is also observed while melanin-containing histiocytes may be present Varying amounts of necrosis are usually seen.

## THERAPY

The many thousands of soft naevi which have been removed by doctors and cosmeticians over the years and the extremely rare occurrence of malig nancy constitute strong presumptive evidence that a single trauma does not

initiate malignant changes. When these are present clinically or microscopically and there is no evidence of metastases surgical excision should be performed with a margin of not less than two centimetres of normal tissue wide of and deep to the lesion.

It is extremely doubtful if surgical removal of regional glands will prevent metastases or even wide excision of the lesion and dissection in continuity as advocated by PACK *et al.* who claim a 15 per cent. to 18 per cent. five year survival rate, since WILBUR and HARTMAN found local recurrence up to nine years after surgical removal and nodal metastases up to thirteen years later. Also the writer has seen local and nodal recurrences up to ten years after surgical excision of several naevi which gave no microscopical evidence of present malignancy. BECKER and others also express doubt as to the value of removal of the glands before metastases occur.



1046. Mixed cell sarcoma.

*(Grennan ey–Sydney)*

If the regional glands are invaded surgical excision followed by irradiation offers the best prospect of benefit, which is usually short-lived, if obtained. It is possible that BODE's fast electron therapy may prove of greater benefit for glandular metastases.

## PROPHYLAXIS

Suspicious looking lesions and those in areas subjected to friction and trauma are best removed by conservative surgery preferably before puberty since malignant changes and metastases rarely occur before then (WEIDMAN, PACK). SPITZ includes among lesions that should be removed before puberty those situated on the palms, soles, scrotum and vulva.

## PROGNOSIS

In the vast majority of cases the prognosis is bad. If microscopic examination reveals packing of the lymphatic or blood vessels with tumour cells, metastases have occurred.

Recurrence of an initial lesion after excision is usually seen within two years, although new lesions may develop within a few weeks or up to fifteen years later (ORMSBY and MONTGOMERY)

Death usually results within two or three years after the occurrence of metastases although ten to fifteen year survivals have been reported.

## MALIGNANT TUMOURS ARISING IN AND BELOW THE DERMIS

### SARCOMA

Sarcomata of the skin are malignant tumours composed of cells derived from the mesoderm. Whether primary or metastatic in origin they are among the rarest of skin malignances and comprise approximately 5 per cent of all sarcomata occurring in the body. They are commoner in the first half of the



1047 Generalized lymphosarcoma.

life cycle and very malignant lesions have been observed in infants even shortly after birth (ELLER). If the tumours are comprised of cells whose character is sufficiently pronounced to recognize their original structure they can be classified accordingly *e.g.* fibrosarcoma or angiosarcoma. If this is not

possible they can be designated according to the type of cell present e g large or small round or spindle cell mixed cell and giant cell sarcoma. Melanosarcomata are believed by some to arise from the clear cells situated in the basal layer of the epidermis (BECKER and OBERMAYER). It has been stated that the only primary cutaneous sarcomata are those which arise from the blue naevus of Tièche and even Mongolian spots but it is doubtful if this has ever been observed to occur *Myxomata* are of special interest, as they are not only potentially malignant, but also frequently have been observed in some native populations (TEN SELDAM)

As the regular observation of neurofibromatosis amongst Indonesians seems to indicate that von Recklinghausen s disease is less rare in these people than in whites it might well be that sarcomata developing from this disease also have a special importance (VOS, REDDINGIUS, TEN SELDAM)



1048 Idiopathic multiple haemorrhagic sarcoma (*See also Figs 134 135 and 137*)

## AETIOLOGY

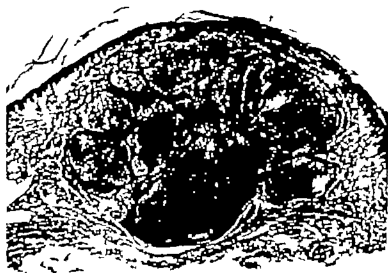
The cause of sarcomata is unknown. They are observed increasingly in North Africa and their incidence appears to increase as the tropics are approached (MUSINI-MONTPELLIER). Trauma appears to play some rôle. There are no presarcomatous lesions analogous to precarcinomatous ones but certain growths on rare occasions, may be the points of origin for sarcomata e g von Recklinghausen s neurofibromata scars, chronic radiodermatitis and angiomata.

## SYMPTOMATOLOGY

Round and spindle cell sarcomata begin as small firm, freely movable cutaneous or subcutaneous nodules and grow slowly to a size varying from

a cherry to an orange or larger. The overlying skin is smooth and may be normal in colour, bluish, bluish-red or telangiectatic. Sometimes there may be ulceration with vegetation. The lesions which may be single or multiple may remain localized for years but a change in character may take place at any time.

Many giant cell tumours of the gum (epulis) are benign, the giant cells being of foreign body type. Malignant ones commonly involve the bone. In fibrosarcomata the large cell type is more malignant than the small cell type but in lymphosarcomata the reverse is the case. Angiosarcomata have a bluish colour which may vary from dark violet to green and yellow due to a



1049 Kaposi's haemangiosarcoma. Fibrous tissue trabeculae are seen dividing up the foci of angiosarcomatous tissue.
*(Kaminer and Murray—Johannesburg)*

tendency to haemorrhage. Malignant haemangioendotheliomata are of firmer consistency, may ulcerate and are locally malignant but rarely metastasize. Lymphangioendotheliomata rarely ulcerate or metastasize. *Generalized sarcomatosis* is unusual, progress is slow and eventually death is likely to ensue. *Lymphosarcomata* may be single or multiple or occur as a chain of enlarged lymphatic nodes. Death usually occurs in a few years although metastases are uncommon in the viscera.

*The differential diagnosis* is the same as that for squamous cell carcinomata.

UNDERWOOD *et al.* believe that practically all new growths which develop after radiotherapy and are diagnosed as sarcomata will prove on thorough microscopical examination of multiple sections to be squamous cell carcinomata.

## THERAPY

Lymphosarcomata are radiosensitive but recurrences after therapy are common. Orally administered arsenic may be of assistance. Other sarcomata tend to be relatively radio-resistant. For these scalpel excision, cautery or diathermy is to be preferred assisted, in cases difficult to remove completely by irradiation.

## PROGNOSIS

The prognosis as to life is usually good in the early stages. Solitary lesions treated adequately do not recur as a rule. Should recurrence take place metastases commonly follow with a bad prognosis. Round cell sarcomata and those with undifferentiated cells may be highly malignant. Generalized sarcomatosis is usually fatal.

## IDIOPATHIC MULTIPLE HAEMORRHAGIC SARCOMA (Kaposi)

This condition is a rare one and the cause unknown. It occurs as frequently among Negroes as among Whites (HAZEN and FREEMAN). The possibility of a genetic factor has been suggested (KAMINER and MURRAY)

The lesions usually appear first on the extremities especially the legs but may occur anywhere. They appear as reddish, purplish or bluish nodules or plaques or diffuse infiltrations of a rubbery to firm consistency The eruption is usually bilateral. Nodules may be discrete grouped or confluent and may or may not be painful. Ulceration is uncommon. There may be a boardy swelling of the hands and feet, an appearance of elephantiasis, or a marked oedema particularly of the lower extremities Tumours may be soft or surrounded by telangiectases, and purpuric, cystic, bullous and verrucose lesions have been described. The course of the disease is slow with new lesions increasing in size and others involuting leaving atrophic, depressed and pigmented areas. Involvement of adjacent glands may take place. There is a tendency to recurrent haemorrhages which terminate in pigmentation of varying colours The blood count may present some degree of eosinophilia and monocytosis and involvement of internal organs has been reported (PAUTRIER and LASSER). *Diagnosis* has to be made by biopsy from sarcoid, syphilis leprosy mycosis fungoides angioma angiofibroma sarcoma, malignant melanoblastoma, pyogenic granuloma and lymphoblastoma.

## PATHOLOGY

This is a form of angiosarcoma with a very varied histological picture. The interpretation of a given slide may be extremely difficult. In the early stages clusters of capillaries are present, not only in the corium close to the epidermis, but also in the

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# MISCELLANEOUS

# AND EPILOGUE

CHAPTER 98

# ADENITIS AND MIXED ADENITIS

R. D. G. PH. SIMONS – Amsterdam
K. GREENWOOD – London

Since swellings of the lymph glands are very frequent in the tropics it will be useful to add a brief survey concerning adenitis and mixed adenitis.

The following factors should be kept in mind in every case of adenitis.

1 Whether the adenitis is general or solitary
2 Localization (differentiating especially between femoral and inguinal adenitis)
3 Whether or not the adenitis is painful
4 Whether any *periadenitis* is present it causes the bubo to adhere to the overlying skin which becomes inflamed (the skin is hot to the touch and coloured a reddish violet)
5 Whether the bubo is (a) solid or (b) softened "en bloc" or (c) contains only small, softened areas ("multilocular softening")
6 Whether a primary lesion or a "porte d'entrée" of the infection can be found if not, the French speak of a "bubon d'emblée"
7 General signs, if any as well as the condition of the iliacal lymph glands, the liver and the spleen the results of WASSERMANN's ITO's and FREI's tests etc.

## GENERAL ADENITIS

General adenitis may occur in

1 *Secondary syphilis* The primary lesion may still be present (in the

female often difficult to trace) Other secondary syphilitic lesions may be present. Blood tests are almost always positive.

2. *Bubonic plague* This disease has been described in a separate chapter The buboes which are painful and accompanied by periadenitis, are most frequent in the groin and axilla (often unilateral). They may suppurate and burst, discharging a foul smelling pus Bacilli



1050 Suboccipital adenitis is usually due to pediculosis capitis.
*(Siemens–Leyden)*

may be found in the early stages Petechiae, purpura and gangrene may follow The liver and spleen are enlarged.

3 *Tularaemia (due to B tularense)* This reveals a general painful adenitis and periadenitis simultaneously with febrile arthritis and malaise The glands which adhere together and to the surrounding tissues may suppurate allowing creamy pus to escape. A primary lesion, *e g* a nodule or an ulcer of the finger followed by a rosary like lymphangitis may be present. A multiforme-like papular or pustular rash may occur in the second or third week of the

disease. Smears from the lesions are usually negative for the bacilli.

The FOSHAY Intradermal test (early) and agglutination tests (3rd week of the disease) are positive. There is an ophthalmic form of tularaemia with suppurating auricular glands as well as a visceral type from eating infected rabbit meat, manifesting itself by high fever pain in the chest and intestinal complaints.

4 *African Trypanosomiasis* Transmitted by various species of the tsetse fly—genus Glossina) The acute disease reveals adenitis



1051 Unilateral adenitis and periadenitis in tuberculosis.

with fever exanthemata, and transitory oedema. The chronic form is the result of invasion of the nervous system and results in wasting, and physical and mental apathy leading to coma.

Diagnosis depends on the demonstration of the trypanosomes in the blood, in lymph glands or in the spinal fluid. Positive blood findings are rare.

5 *South American Trypanosomiasis (Chagas's disease)* An uncommon disease caused by *T Cruzi* and transmitted by the reduviid (cone nose) bug In the acute stage, there is fever, oedema, anaemia and polyadenitis. The acute form is more common in children

and young adults. The liver and spleen may be enlarged. Diagnosis depends on the demonstration of trypanosomes in the blood (uncommon in the later stages) or of leishmania muscle fibres, or by the MACHADO complement fixation test. Lymph nodes and spinal fluid are usually negative for trypanosomes.

6. *Rat-bite fever* (Due to Spirillum virus transmitted by the bite of an infected rat) The disease is characterized by a local inflammatory reaction at the site of the bite, which may become ulcerated, lymphangitis lymphadenitis fever joint pains and various rashes particularly purplish maculo-papules on the chest and upper



1052. Submandibular pseudo-adenitis actually a sporotrichotic gumma. *(Nunes Andrade–Moura)*

arms Diagnosis is by dark-ground microscopical examination of blood or of material from an infected lymph node in the early stages or by animal inoculation.

7 *Melioidosis* This is a very rare condition derived from rodents due to the organism *Pfeifferella whitmori* and it is described in Vol I About one hundred cases have been reported in the literature to date There is an acute septicaemic type with a ninety five per cent mortality and an extremely rare chronic type in which large sluggish abscesses may occur in any organ of the body and in which death is delayed for months or years.

8 *Scrub Typhus* Regional lymph glands are enlarged and tender

there is general adenopathy associated with fever, headache, epistaxis, and a rash which appears about the fifth day

9 *Dengue* In many cases the cervical and inguinal glands are swollen. (See Chapter 28).

10 *Filariasis* These conditions, due to various microfilariae, are treated in volume I of this book. Marked lymphadenitis particularly in the inguinal region, may occur in addition to lymphangitis,



1053. Inguinal and femoral adenitis in bubonic plague.
*(Bonebakker–Rotterdam)*

orchitis, epididymitis, elephantiasis and secondary pyogenic infection. Microfilariae may not be demonstrable in the peripheral blood, in which case a clinical diagnosis may have to be made.

11 Tuberculous adenitis or *scrofula* is most frequently localized in the posterior cervical area There is periadenitis and liquefaction of the diseased gland, resulting in rupture The MANTOUX test is positive Oral B C G vaccinations may cause cervical adenitis intracu

taneous vaccination, axillar or inguinal adenitis and periadenitis.

12. *Sporotrichosis* This disease is fully dealt with in Chapter 79
13. *Prurigo Hebrae* This disease is dealt with in Chapter 102.
14. *Hodgkin's disease* which generally occurs in the male between 20 and 40 years, reveals a chronic multiple painless adenopathy without periadenitis. Anaemia, pruritus and urticaria usually occur. The cause is unknown. The condition leads to death within a period of three years.



1054 Bilateral adenitis due to microfilaria malayi.

15. *Other lymphoblastomas* such as leukaemia, mycosis fungoides which are probably genetically related to HODGKIN's disease and lymphosarcoma may also reveal adenitis as has been described under No 13.

**SOLITARY ADENITIS**

1. In the neck this disease is usually due to pyogenic infection of the scalp e.g. in pediculosis.
2. In the cervical area it is most probably due to tuberculosis.
3. In the armpit(s) it is most frequently due to some pyogenic infection of the arm(s). Suppurating axillary adenitis may be of tuberculous

origin. When acute the diagnosis of plague should be considered. A non-inflammatory form may indicate cancer or lymphoblastoma of the breast. (The axillary adenitis should not be confused with hidradenitis of the apocrine glands.)

4 In the bicipital fold solitary adenitis almost certainly indicates secondary syphilis particularly if the adenitis is painless and not accompanied by periadenitis.



1055 Bilateral adenitis due to filaria bancrofti. (No elephantiasis of the legs).

5 In and below the groins (inguinal and femoral) See under general adenitis. Furthermore

A *Pyogenic infections* of the genitals (*e g* secondarily infected scabies of the penis) and of the foot (*e g* secondarily infected athlete's) foot may lead to uni or bilateral adenitis with or without slight periadenitis (inguinal or femoral). In very rare cases the pyogenic adenitis may resemble the bubo of lymphopathia venerea (lymphogranuloma venereum) (See Vol. I).

B. *Filaria Bancrofti's femoral buboes.* The firm femoral gland, usually located on the non-elephantiastic leg may or may not be accompanied by periadenitis.

C. *Buboes* in carcinoma of the genitals and from lymphoblastomas are solid, often indolent and unaccompanied by periadenitis.

D. *Bubonic plague,* which first manifests itself in the groin, starts with a unilateral, very painful bubo. The patient lies with the affected leg slightly drawn up. (See also under general adenitis).

E. *Venereal adenitis*[1]

a. *Satellite adenitis* is a name for the bubo in primary syphilis.



1056. Satellite adenitis in primary syphilis.
*(Siemens–Leyden)* [illegible]

It is indolent and not accompanied by periadenitis. WASSERMANN's blood test usually is or will become positive.

b. *Symphathetic adenitis* refers to the bubo in chancroid. There is in addition painful periadenitis and suppuration "en bloc". ITO's test is positive.

c. *Bubon d'emblée* is the bubo in which the primary lesion cannot be seen. This is possible in primary syphilis but

[1] Venereal buboes must not be confused with those caused by foot lesions (sometimes merely an unimportant case of athlete's foot), scabies of the penis, prurigo, HODGKIN's disease, leukaemia, plague, cancer etc. Quite possibly there may also exist mixed non-venereal and venereal mixed buboes.

the bubon d'emblée par excellence is seen in NICOLAS FAVRE's lymphopathia venerea. It is painful, there is periadenitis, multilocular suppuration and swelling of the iliacal lymph glands. FREI's test becomes positive after two weeks or later.

d. *Gonorrhoeal bubo* is a cord-like swelling which readily responds to penicillin. Gonococci cannot always be found and there may be no discharge from the urethra either.





1057. Chancroid bubo, suppuration en bloc.
(Fasal, San Francisco)

1058. Lymphopathia venerea, multilocular suppuration resulting in fistula formation.
(Fasal-San Francisco)

e. *Phagedenic and gangrenous ulcers* of the penis, and the venereal as well as the non-venereal acute ulcus vulvae from infection with B. crassus (which should not be confused with chancroid) often cause only slight adenitis, much less than one would expect.

**MIXED ADENITIS**

Mixed adenitis is often overlooked, but the following combinations are not too rare

(a) Chancroid and syphilis ( two-in-one bubo). If a chancroid bubo relapses" being solid and not so painful" it will be a supervening syphilis because of its longer incubation period.

(b) Chancroid and lymphopathia venerea (" two-in-one" bubo) In this case the relapsing bubo will be accompanied by iliacal adenitis.



1059 R lapse of lymphopathia enerea in old scar

(c) Chancroid, primary syphilis and *lymphopathia venerea* (" three-in one" bubo)

(d) An additional gonorrhoeal bubo may be present but this is a somewhat theoretical case.

(e) Syphilis and lymphopathia venerea. This combination is not too uncommon.

(f) Syphilis followed by chancroid. Although rare it might be possi

ble that a syphilitic adenitis becomes mixed with a chancroid infection from a later infection before the occurrence of the syphilitic chancre, since the incubation period of the latter is shorter than that of the former.

(g) Lymphopathia venerea and syphilis.

(h) So-called "hybrids" i.e. a venereal bubo "mixed" with a non-venereal one.

Adenitis is not invariably preceded by a clinically distinct mixed genital ulcer (e.g. adenitis mixta in lymphopathia venerea with chancroid or syphilis, and GOUGEROT's "chancrello-syphilis sans chancre mixte").



1060 Pseudo-adenitis in metastasizing malignant melanoblastoma.
*(Ten Seldam–Sydney)*

# AINHUM
## or dactylolysis spontanea

R. D. G. PH. SIMONS – Amsterdam
G. GONZÁLES PERIS – Havana

### DEFINITION

Ainhum, meaning "to saw" (Nago language) implies the odd condition of one of the toes being annularly constricted and eventually amputated. The cause is unknown. Similar conditions have been seen in leprosy, syringomeylia when termed pseudo-ainhum. Synonyms are *Dactylolysis spontanea*, *Banko-kerende*, *Sukha-Pakla*, *Quijila* and other native terms.

### HISTORY

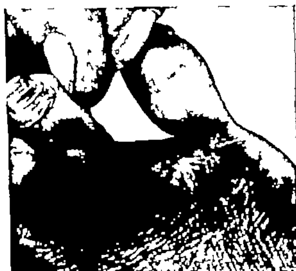
The condition was firstly described by CLARKE in 1860 on the Gold Coast. He termed it "gangrène sèche du petit orteil". In 1867 DA SILVA LIMA discovered ainhum in Brazil.

### EPIDEMIOLOGY

Ainhum has been described in Africa, India, China, South America. It may occur familially. Almost all cases published up to date were observed in individuals belonging to the black race (MADDEN, PARDO CASTELLO and MESTRE, CLARENCE R. BENNETT, M. THOMAS and TUNICK). SPINZIG states that the disease occurs more frequently in men, at the age between 30 and 35 years (GERALD A. SPENCER, MESA RAMOS *et al.*, GONZÁLES PERIS *et al.*). However USSERY reported four cases in members of the white race, while ORDIE SHAFFER described one case in a white diabetic woman. BLANKSOHN found a case in a Negro who had always worn shoes. (See Symptomatology).

**AETIOLOGY**

The cause is unknown. Various hypotheses include trauma, filariasis, tungiasis, scleroderma, yaws, leprosy tertiary syphilis etc. In a great number of cases presenting leprous symptomatology this coincidence proved to be merely casual. The same applies to the cases with syphilitic symptomatology The former were described by PARDO CASTELLÓ and MESTRE, while the latter were observed by BLOOM and NEWMAN. On the other hand, SALAZAR CRUZ considers the probability of some relation between ainhum and sickle cell anemia. USSERY

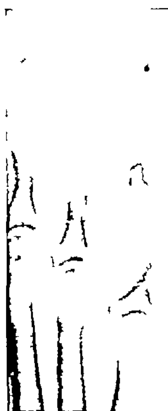


1061 Ainhum in a Negro sailor having always worn shoes.
*(Dermat Clin Univ – Amsterdam)*

asserts that it is not a congenital disease, as seen in the cases reported by PARDO CASTELLÓ and MESTRE, occurring in a family with hereditary palmar and plantar keratoderma (the coincidence of ainhum with this disease being observed in a sibling and a nephew), in which ainhum always appeared in early youth or adolescence. ZAMBACO PACHA considers it as a monosymptomatic form of leprosy and DA SILVA LIMA as a band-like annular scleroderma." The fibrogenetic constitution of the Negroes seems to promote the appearance of the disease" FINDLAY

regards ainhum as a naevoid deficiency which is always accompanied by hyperkeratosis in contrast to pseudo-ainhum from nerve damage. The condition should be distinguished from concentric bone resorption in ainhumoid leprosy (COONEN and CROSBY).

Trophoneurosis is noted as one of the constitutional factors



1062. X-ray photograph of the previous cases showing primary involvement of the bone.

*(Berlanda—Amsterdam)*

(GROS). Several cases with palmoplantar hyperkeratosis and ainhum have been reported in the literature (HYDE and MONTGOMERY, GRACHILBIN, SUTTON and SUTTON, PARDO CASTELLÓ and MESTRE and GERALD A. SPENCER).

## SYMPTOMATOLOGY

Ainhum usually begins with a fissure, which results in osteitis, although the osteitis may occur simultaneously and perhaps even primarily. Sooner or later the fissure becomes annular and the toe becomes



1063 Ainhum and atrophy of the neighbouring skin.



1064 Ainhum and shortening of the fourth toe.

constricted. The condition is most frequently seen at the little toe(s). It may last for years and is painless. It is always accompanied by hyperkeratosis (FINDLAY, MIANI, RASPONI, etc.). WEINSTEIN described ainhum in three, SIMON in two generations of a family. HYDE, MONTGOMERY, FINDLAY, WIGLEY, VOHWINKEL, DRUMMOND and BLUEFARB

described cases of finger ainhum in European girls and in one Negro boy (FINDLAY). The little finger was affected in all cases, then followed the index and the thumb. Keratosis and knuckle pads may be present. A. FACIO quotes a case of CHALMERS, in which all toes were affected. Similarly involvement of the fifth, fourth and third toes are mentioned by VAUGHN, ROWSER and SHROPSHIRE. QUIROGA and CALZETA quote a case with affection of the ring finger and little finger. However, the most frequent site is found in the fifth toe of one foot or both feet.

#### HISTOLOGY

FINDLAY reported a downward pointed dipping of the stratum corneum with much thickening at the level of the fissure. The stratum lucidum was widened in the fissure. The surrounding plaque of clinically hyperkeratotic skin showed essentially the same structure as the keratosis described above, except that a stratum lucidum was evident, and the corium showed some papillary oedema and a vertical disposition of dense collagen with slight perivascular infiltration of mononuclear cells. Fairly diffuse fibroblastic activity is also noted.

#### THERAPY

Probably footwear will prevent ainhum. DA SILVA LIMA recommends in the early stage of the disease, a vertical incision of the constricting ring, which is also proposed by KEITH and SIMON and GONZÁLEZ PERIS and his collaborators. However later on amputation becomes necessary.

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There is no known therapy for the so-called filarial form. Perhaps hetrazan will prove beneficial.



1065. Craw-craw according to GOUGEROT
*(Encycl. Médico-Chirurg.)*

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CHAPTER 101

# BRAZILIAN PEMPHIGUS[1]

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## DEFINITION

Brazilian pemphigus is a chronic, probably contagious form of pemphigus which occurs most frequently between the ages of 10 and 30. The aetiology is unknown. The disease is endemic in Brazil. Synonyms are *Pemphigus foliaceus*, *South American pemphigus*, *tropical pemphigus* and *wildfire*. The name "wildfire" is a popular one for which there are two explanations: one of these is the burning sensation felt by the patient; the other is derived from the legend that the natives blow the disease on to their foes by means of a magic tube.

## HISTORY

The first cases of endemic Brazilian pemphigus reported in Brazil were those of Paes Leme, but he confused the disease with tinea imbricata.

The chief papers published on the subject are those of Vieira, Orsini de Castro, Rabello, Aranha Campos.

## EPIDEMIOLOGY

The disease occurs most frequently in tropical and sub-tropical regions. The chief foci in Brazil are the interior regions of the States of

[1] Since Brazilian pemphigus is still a non-classified dermatosis, and not yet definitely regarded as a type of any of the other skin diseases, a description could not well be omitted from this book.

Minas Gerais, S Paulo Goiás and Mato Grosso The zone of the greatest incidence lies between 60° and 40° West of Greenwich and between the 15th and 24th parallels of latitude.

Familial cases have been reported. The disease may occur in well-nourished individuals and among all social classes. It appears at all



1066. Brazilian pemphigus (Senear Usher syndrome in Brazil) Seborrhoeic type.

ages but chiefly between 10 and 30 especially at puberty particularly in women, who are more prone to the disease than men (65 %). There is no racial predilection.

## AETIOLOGY

The aetiology of Brazilian pemphigus is unknown. Among the theo-

ries of causation are the nutritional, the allergic, the enzyme genesis (hyaluronidase) the solar the microbial, the endocrinic and the virogenic.

Most Brazilian specialists regard the disease as being infectious, particularly because of the familial occurrence

**CLASSIFICATION**

Some authorities believe the disease to be the same as CAZENAVE'S pemphigus foliaceus while others think it is an autonomous morbid entity

*In its foliaceous herpetiform and erythrodermic phases it is very*



1067 Brazilian pemphigus psoriasiform lesions.

similar to CAZENAVE'S pemphigus foliaceus, but it differs from the latter in many respects chiefly as regards its endemic character and the occurrence of "frustres" cases

**SYMPTOMATOLOGY**

The disease generally begins on the face, on the chest and back and on the legs though it may start at any part of the skin. The initial lesions are extremely polymorphous such as bullae, vesicles and plaques resembling seborrhoeic dermatitis or psoriasiform parakeratosis or impetigo or eczema or even pompholyx

There are several phases. The phase similar to the Senear Usher syndrome is characterized chiefly by being localized on the medio-facial region and by an erythematoid or seborrhoeic dermatitis which may show bullae, vesicles and psoriasiform elements.

*Nikolsky's sign* may be positive or negative. Brazilian pemphigus presents a clinical picture very similar to that of *Senear Usher's syndrome* except that in Brazilian pemphigus the mucosae are not affected.

The symptoms of the other phases are very varied, for they are at times strictly foliaceus or they may be herpetiform or erythrodermo-exfoliative. There is a predilection for the so-called seborrhoeic regions.



1068–1069 Brazilian pemphigus. Senear Usher type.

Circumscribed or diffuse alopecia and numerous ungueal modifications may occur.

In chronic cases *muscular hypotrophy, ankylosis* and *hydrarthrosis* may occur. In the State S. Paulo osteomalacia has been observed, but in those cases there was an additional vitamin-D deficiency.

Intense localized *pigmentary modifications* or typical melanodermas are frequently mentioned, and palmo-plantar keratodermas, crustaceous verrucoid and papillomatous lesions are observed.

Paraesthetic symptoms such as burning, heat, intense pain, itching or even cryaesthesia are reported.

*The endocrine disturbances* of Brazilian pemphigus are of the greatest interest, for they assume great intensity. Amenorrhoea is present only

in women suffering from the advanced generalized form of the disease Atrophy of the breast with modification of the feminine aspect also occurs as well as slight goitre

The endocrine disturbances of pemphigus in young individuals have been studied by ALVES GUIMARAES, who noticed a disturbance of development as regards weight and structure, especially when the disease was contracted before the age of 15 The patients resembled pituitary midgets.

In three patients the present author noticed that the development of the skeleton was arrested long before the appearance of the cuta neous manifestations of the disease. In one case he found a reduction in size of the sella turcica, the frontal sinus being so small as to be



1070 Brazilian pemphigus erythrodermatic type.

barely perceptible The hair of such children is generally fine and silky as is usually the case in pituitary midgets The patients have doll like *faces in which, under the suffering mask of Brazilian pemphigus* delicate lines and fine features persist.

On the sexual side there are noted underdevelopment of the genitals absence of menses and lack of secondary characters As regards gonadal disturbances GUIMARAES and MOURAO found 34.2 per cent of cryptorchism in 35 males examined 68.5 per cent of hypogonad ims 13 5 per cent of azoospermics 10 8 per cent of oligospermics 2.6 per cent of non-spermics 72.9 per cent sexually impotent and 27 per cent with potency sensu latu

### CLASSIFICATION OF CLINICAL PHASES

1. Disseminated form
2. Senear Usher type
3. Foliaceous type
4. Herpetiform type
5. Erythrodermatic type
6. Regressive type.



1071 Brazilian pemphigus ruptured blisters.

### LABORATORY DIAGNOSIS

According to MENDES and ROCHA the biochemical changes in pemphigus foliaceus can be explained by a single process the disturbance of capillary permeability which has been called serous inflammation. In S Paulo AZZI LEAL, MENDES and WANCOLLE studied the metabolism of some mineral salts in pemphigus foliaceus and came to the following conclusions The percentages of calcium and phosphorus in the blood serum were not very different from normal Ca 8.35 to 10 32 mg average 9 67 mg % P 2.42 to 4 5 mg % average

3.35 mg % The amount of chloride in the urine was normal in all tests The authors point out that the determination of the chloride only is not sufficient evidence of abnormal retention of sodium. In all the patients studied the NaCl quotient was very close (0 911 to 1 033) this fact led the authors to conclude that in pemphigus foliaceus there is no abnormal retention of sodium.



1072. Brazilian pemphigus se ere Senear Usher type

The patch tests with potassium iodide are positive. *Cytodiagnosis* (TZANCK) can be employed and histological examination places the dermatosis in the pemphigus group The blood picture varies in the different phases of the disease There is no specific laboratory examination

## HISTOLOGY

The histology is as follows the horny layer is thickened by

hyperkeratosis which involves the follicular ostia there are generally areas of parakeratosis. The horny layers separate from each other as there is no cohaesion and these layers are at times fragmented. There are areas where the horny layer is more or less absent according to the greater or lesser intensity of the exfoliative process. There are usually squamous crusts consisting of parakeratotic laminae among which are



1073 Brazilian pemphigus: foliaceous type.

coagulated serum, neutrophile and eosinophile leucocytes, cellular detritus and bacteria.

However not all these elements are always present. The changes in the granular layer are very constant in some areas this layer is absent while in others there may be thickening due to hypergranulosis in the latter there may be seen thick masses of keratohyalin formed by confluence of the granules such masses fill the cells. In this layer foci of disaggregation are also very common the disaggregated cells show keratohyalin as has just been mentioned. In the superficial layer of

the rete Malpighi foci of acantholysis are rarely absent. The more superficial cells of such foci are swollen, thus protoplasm is abundant, and they are generally basophile with pyknotic nuclei The subjacent cells are elongated, their protoplasm is also basophile and their nuclei hyperchromatic. Above these foci the granular layer is missing and *there is often parakeratosis. Above the papillary apices the rete Mal*pighi is thinned while the inter-papillary crests are hypertrophied by hyperacanthosis. They are either long and pointed or long and broad. They may anastomose and when this process is well marked we call it reticular acanthosis The prickle cells are as a rule swollen. In this layer figures have been observed which may reach the granular layer These



1074 Brazilian pemphigus resembling seborrhoeic dermatitis.

figures vary in direction being vertical or horizontal and in the latter *case superficial.*

Bulla formation is the most important feature of any form of pemphigus even in those cases where clinical blisters are not seen. Contrary to pemphigoid (Duhring's herpetiform dermatitis and benign ocular pemphigoid) where bulla formation is found sub-epidermally bullae are formed in the epidermis in pemphigus. In pemphigus vulgaris and pemphigus vegetans the bulla is formed in the lower epidermis and in pemphigus foliaceus Senear Usher's disease and Brazilian pemphigus the bulla is present in the subcorneal parts of the upper epidermi Still we found sub-epidermal bullae in two of

our cases The basal layer is always hyperpigmented karyokinetic figures are not frequent. Exoserosis as well as intracellular oedema is generally slight. Exocytosis is not intense and consists of neutrophile eosinophile and histiocytic leucocytes, but these three cellular types are not always all present.

There is always papillomatosis of the derma and the papillae are at times long and slender, thus giving the skin a verrucoid aspect.

Dermic oedema is constant and is always more pronounced at the level of the papillary body and the sub-papillary layers it is sometimes marked around the appendices of the skin.

The infiltration of the dermis may be more or less intense and



1075. Brazilian pemphigus in the Negro Hyper and para-keratosis, fractured horny layer Acanthosis and acantholysis. Some parts of the epidermis are atrophic.

oedema is met with chiefly at the level of the papillary body and sub-papillary layers and consists of neutrophile leucocytes, eosinophiles, lymphocytes, and histiocytes the fibroblasts and epithelial cells are usually increased in number

There is also vascular ectasia. As regards the elastic network elastorhexis and diminution of fibre are noted

The dermic oedema and infiltration may spread to the hypoderma. The organs of the skin may show changes such as folliculitis oedema of the external radicular sheath, increase of sudoriparous glands and atrophy of the sebaceous glands.

## DIAGNOSIS

Brazilian pemphigus should be distinguished from DUHRING's disease, pemphigus vegetans, lupus erythematosus impetigo eczema, seborrhoeic dermatitis and other bullous dermatoses.

In "frustes" cases diagnosis is sometimes difficult, histological examination being necessary

## EVOLUTION

The Senear Usher phase may be initial or terminal and may also develop into all the other clinical phases or regress to a radical cure or remain stationary for an indefinite period The same thing occurs in the case of patients with scattered lesions which may later show a medio-facial localization.

In the Senear Usher phase the medio-facial lesions may disappear while the others persist.

The foliaceous, herpetiformis or erythrodermic phases may also pass through all the other phases remain stationary or regress to a radical cure. It must be noted that Brazilian authors classify under one heading all the aspects we have described, for the patients always come from the same foci and thus I have verified over a period of 25 years by means of photographs

The evolution of Brazilian pemphigus is in most cases chronic and torpid it lasts for 5 to 20 years but may cause rapid death.

In the period of cachexia the patient paradoxically seems better as regards the skin lesions, but there occur bedsores and a complete breakdown of the organic defences the patient dies of some intercurrent disease

The contrast between the regressing skin symptoms and the progressive general symptoms which cause death was also noted in European pemphigus foliaceus by GOUGEROT BENDA and VARAY

## COMPLICATIONS

Complications and intercurrent diseases are more common in advanced cases. These complications affect chiefly the digestive system, the lungs the skin itself and the kidneys.

The digestive system is usually the first of the great visceral systems to show serious functional disturbances The most frequent of these

is diarrhoea which may be transient or permanent. Transitory diarrhoea is usually due to disregard of the prescribed diet, to some modification not well tolerated, or even to emotion. In the upper digestive tract gangrene of the mouth occurs as we ourselves have seen in one case.

In the lung, pneumonia, broncho-pnuemonia and tuberculosis occur In the skin the complications are due to secondary infections and localized traumatic dystrophy (bedsores) which can be averted by constantly changing the position of the patient in bed. As regards the urinary functions there is sometimes hypoazoturia with marked uraemia.

In the eyes, conjunctivitis, ectropion and cataract occur.

### PROGNOSIS

In European pemphigus foliaceus, cure is very rare. In the Brazilian pemphigus, however the prognosis is less unfavourable 40 per cent. of cases are cured either spontaneously or with the help of the more or less empirical methods of treatment adopted. The invasion of the morbid process, which occurs in waves, may last 15 days to a year

The gravity of the disease is in direct proportion to the rapidity of the period of invasion.

Regression when it occurs takes place from the periphery to the centre, *i.e.* exactly contrary to the mode of invasion.

The appearance of papillomatosis or hyperpigmentation is a good prognostic sign. The cases in which these elements appear are called resistance forms.

### THERAPY

Quinine given orally in doses of 1/2 to 1 g is beneficial. Boricated vaseline should be applied Trivalent or pentavalent arsenical preparations are harmful.Bayer s Germanin,sulphanilamide and the diuretic salts of mercury have been given, but great care should be exercised in their use Penicillin even in large doses, has no effect on the disease, but only on the secondary infection. Corticotropin and cortisone represent a valuable therapy although improvement is temporary which necessitates *continuation* of treatment in order to keep the disease in check. Patients get worse when treated with bromides iodides and bismuth are entirely contra-indicated

Coal-tar used locally in collodion and acetones are recommended In "frustes" cases B C.G is being used in doses of 0 20 by the mouth once a week up to a total of 15 doses

### PROPHYLAXIS

Preventive measures are limited to isolation of the sick in special hospitals. Two hospitals for pemphigus already exist in our country one in S Paulo and the other at Ponta Pora in the State of Mato Grosso The Belo Horizonte Public Hospital has an isolation mosquito-screened ward exclusively for the treatment of female sufferers from pemphigus.

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CHAPTER 102

# THE SHIP'S SURGEON AND THE TROPICAL DISEASES OF THE SKIN

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Ship's surgeons often have the opportunity to observe and treat patients suffering from tropical skin diseases. It is not even necessary for a ship's doctor to be in the tropics to be called upon to treat patients with tropical diseases of the skin, for sailors roam the seven seas and visit many ports. Moreover passengers come from every part of the world. At the most unexpected moments a ship's surgeon may be obliged to treat a tropical skin disease, even in territories far away from the equator For this reason a thorough knowledge of these diseases is as necessary as an extensive knowledge of venereal diseases, which are frequent with seamen, and the symptoms of which often resemble so much those of tropical diseases of the skin that confusion is quite possible

We have no exact knowledge of the frequency of tropical skin diseases among seamen or passengers, no more than we know the frequency of their venereal diseases. Three large steamship companies found that in 1946 and 1947 about 16 per cent. of the seamen who came for general examination suffered from a contagious skin disease (for instance scabies) while 7.5 per cent. had active venereal disease These data show the importance of skin diseases and venereal diseases among seamen. They cover moreover only part of the cases, for all are not known[1] However when judging these facts, we should not

[1] The number of seamen suffering from venereal disease is much higher than 7.5 per cent It increases with age and reaches 60 per cent. after the age of 50 Most infections are acquired between the ages of 20 and 30 The youngest case known to me is that of a boy of 15 with primary syphilis.

forget that during and shortly after World War II hygienic conditions were often bad and morals low in many countries.

Which tropical diseases of the skin a ship's doctor will see on his voyages depends on the parts of the world he is going to visit and on the places of origin of the crew and passengers. On ships with a white crew and passengers he will see fewer and other skin diseases than on board ships with coloured crew and passengers.

A ship's surgeon, who regularly goes to and through the tropics, will have more opportunities to study patients with tropical diseases of the skin than one who stays outside the tropical belt. On his voyage to the tropics he will see other skin diseases than on his



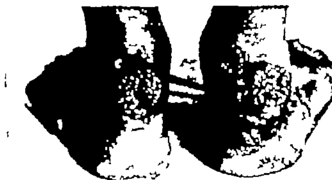
1076 Cutaneous leishmaniasis (ulcerative type)
*(Orig. G. Castle–Bela Herzog)*

voyage from the tropics to a colder climate. Some shipping companies take on board their ships during the voyage along tropical coasts, natives to work in the ports as dockers. These natives may suffer from all kinds of tropical skin diseases. Last but not least it depends upon the knowledge, the experience and the attention of the ship's doctor whether he will be able to diagnose a tropical disease of the skin, for as ROXBURGH states: "*The surest way to miss a diagnosis is not to look for it*".

The way of living on board often increases the chances of getting skin diseases and favours their spreading. Owing to the fact that on board ship passengers and crew live close together there is more

direct contact between people than ashore. The wash-places are often shared, which has a bad influence on bodily cleanliness. High temperature and great humidity cause abundant sweating, which may also cause skin diseases. As we know tropical diseases of the skin occur mostly and are worst, in territories with a moist climate, as along the coasts of East Africa and the Persian Gulf. However, in drier territories skin diseases are not rare either.

To the above-mentioned factors we must add the great influence which the strong radiation of the sun at sea has on the skin and body. It appears from the spectrographical researches of VRY that, from the



1077 Cutaneous leishmaniasis (verrucous type).
*(Orm. G. Costa—Belo Horizonte)*

poles to the equator the ultraviolet rays reaching the surface of the earth increase not only quantitatively but also qualitatively. Moreover the number of hours of sunshine is considerably greater in the tropics than in higher geographical latitudes. The reflection of the light on the surface of the sea also causes the intensity to increase. Moreover passengers at sea in warmer territories try to enjoy open-air life as much as possible and spend much time in the sun, whereas on shore people try to avoid the sun as much as possible. This explains why on board there are comparatively more cases of diseases through actinic causes than on shore. The ultraviolet rays are not the only causes of skin diseases: the infra red rays too are injurious. Besides

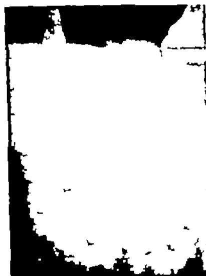
the light at sea is highly polarized. What influence this horizontal polarization has on the skin is insufficiently known.

Every ship's surgeon is sure to meet on his voyages to sunnier regions sufferers from *acute dermatitis solaris* especially among those making their first sea voyage. Dermatitis solaris is caused almost exclusively because passengers and members of the crew who are in the tropics for the first time expose themselves too long to the sunlight when swimming or sunbathing. Fair and red-haired people with little skin pigment may react to unduly long exposure to the sun's rays with violent general symptoms: fever, albuminuria and eosinophilia. If the redness of the skin is not recognized as the consequence of too long an exposure to the sunlight, it may lead to a wrong diagnosis. The clinical picture is mistaken for that of an exanthematous contagious disease, for instance scarlet fever. A patient with acute dermatitis solaris may, however, at the same time suffer from an exanthematous communicable disease. Most errors can be avoided by carefully watching the lesions and their distribution. The French physicians are right when they say: *Pour voir il faut regarder*.

In some hypersensitive people the ship's doctor will be able to observe *eczema solare*, a violently itching papulo-vesicular eczema on those parts of the skin which have been exposed to sunlight, or *Hutchinson's summer prurigo*, a polymorphic eruption, consisting according to the descriptions of MANSON and ROXBURGH of erythema, papules, vesicles, pigmented spots, weeping areas, crusts and small retracted scars on the parts that have been exposed to the sunlight. This summer prurigo may lead to diagnostic difficulties when the picture has been changed by secondary infection and lichenification. There is a diagnostic pitfall here because of the difference between *summer prurigo and summer eruption*. These two dermatological entities which are so much alike, respectively indicate an urticarial papular dermatosis which easily lichenifies and *hydroa aestivale*, a "lucite" or actinodermatosis, which is bullous and sometimes leaves scars when cured (hydroa vacciniforme). This must not be mistaken for *hydroa vesiculosa* as a synonym of *erythema exsudativum multiforme* and *hydroa bullosa* as a synonym of *dermatitis herpetiformis Dühring*. The *prurigo hiemalis Dühring* is an urticarial winter prurigo which is especially found in men on the covered areas of the skin. The summer

prurigo of HUTCHINSON is more common in women and on the uncovered skin—at least according to the literature (DARIER) It is identical with *prurigo solaris* mentioned on page 99 The combination of prickly heat and urticaria solaris would not, of course, be mistaken for summer prurigo For convenience sake, however, many light dermatoses are called summer eruption.

The above leads us to deal with this subject at some length. Prurigo comprises a special group of itching papular dermatoses, the acute



1078. Varicelliform eruption in secondary syphilis.
*(V. an der Zyl-The Hague)*

form of which may moreover be urticarial and vesicular the chronic form is accompanied by lichenification. The name meanwhile gives rise to much confusion among other things with the term pruritus. DARIER in answering his own question "Comment s orienter dans ce chaos?" begins by dividing prurigo into the acute and the chronic form and the latter again into the diffuse and circumscribed forms. *Prurigo simplex acuta* (BROCQ), better known as *strophulus* of WILLAN and BATEMAN is a disease of the infantile skin, which we rarely encounter in the tropics. This affection, formerly ascribed to "teething"

and now mostly considered an allergy against special foods, is perhaps as BOTTER of the dermatological clinic at Leyden suggested, an infectious disease, though this has not yet been verified by experiment.

*Prurigo simplex chronica* consists in the first place of *prurigo simplex chronica circumscripta* or *prurigo vulgaris* which is identical with *lichen* VIDAL or the *névrodermite* BROCQ. The papules which appear in this skin affection are the "dwarf type" of those of *prurigo nodularis* To chronic prurigo simplex further belong *prurigo chronica diffusa* or *disseminata* among which a number of forms must be classed, *viz*

1 *prurigo Hebrae* a strophular eruption, beginning in early youth, which is accompanied by marked enlargement of the lymphatic glands and may last for years.
2. *prurigo nodularis Hyde* an itching macro-papular affection, which is especially found on the extremities but also on the trunk. It resembles *lichen obtusus* very much, if indeed it is not identical with it The aetiology is unknown. This disease is certainly met with in the tropics and a similar if not the same, affection is found as the consequence of scratching due to bug-bites
3 For the sake of completeness a third form of chronic diffuse or disseminated prurigo must be mentioned here, the *prurigo symptomatica* of BESNIER, which chiefly occurs in children and is perhaps akin to prurigo Hebrae. This disease was called *eczema flexurarum* by HEBRA and VIDAL named it *lichen simplex chronicus disseminatus* At present the disease is known in America by the name of *atopic dermatitis* (HILL and SULZBERGER) after the concept "atopy" of COCA. A detailed work about this atopy-concept by NEXMAND appeared in 1948 at Copenhagen. This author assumes that the affection is of an allergic character which corresponds to the definition of the Americans and particularly of COCA who pointed out that atopy is that form of allergy which has a hereditary predisposition and with which specific anti-bodies can be shown after the method of PRAUSNITZ KÜSTNER. *Prurigo lymphadénique* of DUBREUIL as a symptom of leukaemia and HODGKIN's disease are only mentioned here for completeness sake.

After this theoretical digression we return to our subject In many sailors whose skins have been exposed for years to the influence of wind rain and sunshine the ship s doctor can observe *dermatitis*

*solaris chronica*, on the back of the hands, in the face and in the nape of the neck. This sailor's skin is characterized by atrophy marked creasing local pigmentation interspersed with depigmentized spots teleangiectases and hyperkeratosis which have a tendency to malignant degeneration. The back of the neck of most elderly seamen, especially when they belong to the deck staff, mates, boatswains and sailors, show the so-called *cutis rhomboidalis* In Dutch law the dermatitis solaris of seamen is considered to be an occupational disease and is put on the same footing as an accident if it causes incapacity for work.

Dermatitis solaris chronica seldom occurs among the coloured races According to HARDY the colour of the skin is of little importance for the radiating capacity ultraviolet rays are reflected, infra red rays are absorbed. As a dark skin, however has a greater absorbent capacity for thermic rays than a white skin, the temperature of the former rises more quickly and sweating begins sooner. But, considering the fact that the white skin sweats abundantly in the tropics whereas the strongly pigmented skin under the same circumstances is covered with only a thin layer of very small sweat drops, which evaporate quickly we see that much heat is withdrawn from the surface of the coloured skin, in such a way that ultimately the temperature of the dark skin does not rise so much as it does in the white skin. This explains why dermatitis solaris chronica does not occur among people with highly pigmented skin.

Among white people who have lived in the tropics for a long time and have stayed much in the open air the ship's surgeon sometimes finds *dermatosis festonalis frontalis* described by CASTELLANI He gives the following description of it "The dermatosis has a festooned appearance, the margin being slightly raised, often of a vivid red or coppery red colour while the skin which it encircles has a peculiar whitish, occasionally leukodermic appearance and may be slightly atrophied At times small patches of hyperpigmentation are scattered about. There is little or no pruritus, and sensations of pain, heat, etc. are normal This affection is sometimes taken for a disease caused by a fungus, but no one has ever succeeded in finding any fungi Sometimes it is also mistaken for leprosy but there is no anaesthesia. It may also be mistaken for *eczema frontis* which some people suffer from

through wearing a hat or a cap covered on the inside with a leather strip which may have been tanned with chromic salts.

Many passengers and seamen suffer from *prickly heat* during a voyage through the tropics particularly the engine room staff engineers oilmen, firemen and trimmers. Some members of the crew struggle every voyage with this evil. Even the ship s surgeon does not remain free from it. This annoying disease may last a considerable time after the victim has left the tropics. Prickly heat is sometimes considered to be an occupational disease. If it causes incapacity for work, the affection is put on the same footing as an accident and the victim receives accident benefit and free medical treatment during the time of his incapacity

An inexperienced ship s doctor sometimes mistakes prickly heat for scabies or what is worse, scabies for prickly heat. In the latter case this may cause a very undesirable spreading of scabies, either on board or after the seaman has come back home. By careful observation of the characteristic symptomatology and the different distribution of the two affections the ship s doctor can avoid errors. Scabies and prickly heat may occur at the same time. The ship s surgeon should keep this possibility in mind.

In a cool climate *hyperhidrosis* is mostly a functional disease. In the tropics and on board ship this is different. As about 15 % of the total loss of heat by the perspiratio insensibilis is from the skin of the hands and feet and the loss per surface-unit of skin of these parts is about three times as high as that of the remaining area, high demands are made upon the function of the sweat glands of the hands and feet in the tropics We see therefore that in tropical regions and on board ship many people who in a cooler climate are never troubled with perspiring hands or feet, complain of this The engine room staff and the cooks suffer particularly Oedematous swelling of the epithelial cells of the ducts of the sweat glands in the palms and soles block these ducts which causes sweat retention. A vesicular eruption then develops on the hands or feet or both, the *tropical pompholyx* Careful examination reveals that in many cases this disease is not primarily a sequence of a disorder of the sweat glands but that its aetiology is either an eczema or a dermatitis through external causes or an infection due to special fungi or that the affection is the result of a toxic eruption.

Owing to the thickness of the stratum corneum the vesicles cannot burst as they would do on other parts of the skin. Therefore they remain in the skin giving the impression of grains of hempseed under the epidermis.

Occasionally the ship's doctor may find that urticaria have been caused by actinic stimuli. As there are, however, on board and in the tropics many other possibilities that can produce urticaria, the ship's surgeon should be very careful about diagnosing urticaria through actinic rays.

Among the engine-room staff boils are often seen especially on the trunk and in the lumbar region. Furunculosis is often found in

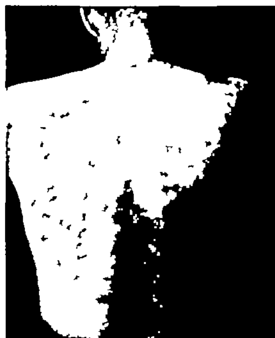


1079 Vegetant pyoderma in the groin.
*(Osr G Carta-Bela Hart-mann)*

other people on board too. Sometimes a regular epidemic of furunculosis may rage on board. The boils are often accompanied by lymphangitis and lymphadenitis.

Engineers, oilmen, stokers and trimmers often come into contact with mineral oils, which cause many occupational skin diseases, first and foremost acne. This occupational acne is characterized by its symmetrical distribution over the arms and legs, though the back and chest are not free from them. Unlike acne vulgaris, oil acne leaves the face free, as well as the popliteal spaces. PROSSER WHITE distinguishes three stages which he describes as follows: "The skin is

stippled by hundreds of regularly arranged, minute, projecting, black centred, reddish pimples From these develop secondary typical discrete rounded, well raised, hard papules and pustules of a dusky red colour. These inflamed follicles are at first few and very regularly dotted over the affected limbs, but soon become more general. They vary in size from a pin s head or a hempseed to that of a split pea, and are indolent, form slowly and take many weeks to recede. Ultimately



1080 Oil acne in ship s engineer
*(Simons– Amsterdam)*

the whole nodule gradually and painlessly suppurates and is discharged The hair follicles become completely destroyed and pitted scars are left "

Acne occurs among about 10 of the older stokers trimmers and oilmen I cannot share COLLIS and GREENWOOD s view that acne does not occur among Negroes This disease is repeatedly found among

them, though to a slighter degree than among white people. In addition to acne, multiple sebaceous cysts on the scrotum are often found amongst the engine-room personnel. I never saw malignant epitheliomata there.

Mineral oil may cause acute and chronic inflammations of the skin of those of the engine room personnel who are sensitive to it. Moreover thickening of the skin by hyperkeratosis may occur.



1081 Tinea versicolor in a Javanese.
*(Siemens–Amsterdam)*

The insoluble type of cutting oils, which are used as lubricants seems to be the major cause of folliculitis, oil acne, and even furunculosis (KLAUDER, MORRIS and MALOOF).

Cooks, butchers and other personnel working in the galley pantry and scullery often suffer from paronychia, whitlows and erysipeloid of the fingers. Very often these affections must be distinguished from infections with fungi and sometimes from extragenital chancres.

Leprosy and yaws may give rise to great diagnostic difficulties on board. With a coloured crew and passengers the ship's doctor must always think of these possibilities, but these diseases may also occur among white people, born and bred in the tropics or who have resided there for a long time. These affections must often be distinguished from syphilitic eruptions of the skin. For the differential diagnosis the reader is referred to other chapters in this book. The ship's doctor must bear in mind, however, that a sufferer from leprosy may also have syphilis, a sufferer from syphilis may have yaws. According to HERMANS and others the latter combination is not in-



1082. Psoriasiform yaws of the sole of the foot.
*(Aars-Caraque)*

frequent. The frequent occurrence of tropical ulcers, especially among the natives on a coastal trip, must be mentioned. This must be taken into account in the differential diagnosis.

Affections caused by fungi take a very important place among the skin diseases met with on board. BUTLER, HOUGHTON and COOPER found by examination of a great number of members of the U. S. Naval Service on tropical duty that 33.2 % suffered from skin diseases caused by fungi. The number of infected officers was considerably higher than that of other ranks, viz. 81.8 % against 23.5 %. According

to WEIDMAN and co-workers, 8 % of all the personnel of the Army and Navy admitted to hospitals during World War II, were suffering from skin diseases Among these the skin affections caused by fungi took second place The total percentage of infected people is estimated to be as high as 65 %

Diseases caused by fungi may sometimes be so frequent on board ship that we may speak of an epidemic. It is therefore necessary for the ship's doctor to be perfectly familiar with the technique of the microscopic detection of fungi.

*Pityriasis versicolor* is often met with among the passengers and crew *Erythrasma* too belongs to the frequently occurring skin diseases The latter two affections can mostly be diagnosed only from their outward appearance. The disease caused by a fungus which occurs most frequently on board is athlete's foot or *tinea pedis* This affection occurs in three forms 1 a vesicular 2 a squamous and 3 a pyodermatic form. The vesicular form may sometimes resemble pompholyx and be mistaken for it. Athlete's foot is found in many seamen, particularly in younger ones. Older seamen become more or less immune to it. The disease causes more trouble in hot weather than in cold, consequently in the tropics the suffering is greater than in temperate zones. That this contagious skin disease can spread rapidly is in consequence of the fact that wash-places and shower baths are in common use on board. The wooden floor slats and the bathroom mats contain the fungi and their spores

BUTLER, HOUGHTON and COOPER could find fungi in only 68 7 % of their cases HOPKINS in 70 % of his. He supposes that in the negative cases the infection is caused by *Staphylococcus aureus* or that it is a consequence of a hypersensitiveness for *S aureus* boot-polish antiseptics, etc The infection is furthered by trauma and stasis.

In people working in the galley and pantry stewards and cooks and also in laundrymen, who through their work are much in contact with water the ship's doctor sometimes finds *mycotic paronychia* This condition may give rise to diagnostic difficulties as it very much resembles erysipeloid. Sometimes an extragenital venereal primary lesion is taken for a mycotic paronychium. Microscopic examination will solve the problem.

*Tinea inguinalis* and *tinea corporis* often occur on board among all

ranks and stations and among all races. It would mean quite a long list to enumerate the diseases for which these affections may be mistaken. As the knowledge of skin diseases increases, the number of possibilities of which we can think becomes greater. This does not mean that we must start on our voyage with little diagnostic luggage.

*Trichophytosis* are also found frequently on board, mostly in children but also in adults. Among Negroes the ship's surgeon often sees



1083. Wide-spread infection by Trichophyton rubrum.
*(Pierr Nairobi)*

people suffering from *tinea imbricata* which sometimes resembles *ichthyosis*. Perhaps it is necessary to state here that cases of persistent pruritus ani are often of mycotic origin. Specific treatment cures these patients in a remarkably short time. *Trichosporosis* is found in white as well as in coloured people on voyages to Africa, Indonesia, India, Brazil, Colombia or Uruguay, particularly in natives of these regions and seamen who often go to these countries. *Maduramycosis* and *blastomycosis* are only seen among natives, though, according to MARTIN

and SMITH the latter infection is not very rare in North America

On voyages to South America the ship s doctor sometimes has the opportunity to examine sufferers from *carate s pinta* (mal del pinto)

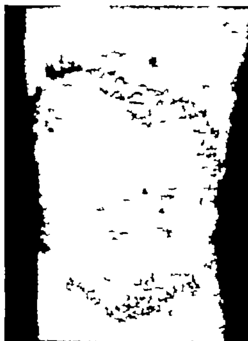
Besides the people who suffer from skin diseases caused by external agents, the ship s doctor may also meet patients on board who suffer from skin diseases brought about by internal tropical diseases Some of these affections are accompanied by more or less characteristic eruptions which the ship s doctor must pay attention to Schistosomiasis, ankylostomiasis, bilharziasis, dengue, tsutsugamushi, leishmaniasis, trypanosomiasis, pellagra and many other clinical entities are examples of internal tropical diseases, characterized by more or less typical dermal symptoms. The reader will find a detailed description in other parts of this book.

In conclusion of this enumeration of skin diseases which the ship s surgeon may meet with, attention must be drawn to a few toxic eruptions of frequent occurrence. Owing to the increasing use and abuse of sulphonamides—some passengers and members of the crew take these drugs on their own initiative—drug eruptions are not rare According to GOODMAN and GILMAN toxic eruptions after taking sulphanilamide occur among 1 9 of those who have taken it after the taking of sulphapyridine among 2 ° after taking sulphathiazole among 5 % SIMONS states that after taking sulphadiazine about 3 % of those who had taken it showed toxic eruptions of the skin These toxicodermas may have a variable appearance a maculopapular rash with high fever appears generally from four to twelve days after the drug has been ingested an eruption resembling measles or scarlet fever may appear after ten or twelve days. Urticaria, angioneurotic oedema petechiae, purpura and exfoliative dermatitis caused by sulphonamides have been observed.

The growing use of penicillin on board also increases the incidence of penicilloderma. Early as well as delayed reactions occur Urticaria, angioneurotic oedema, pruritus pompholyx, exanthematous and eczematoid reactions have been described by several authors. Neither should one forget the skin reactions after the use of quinine salts taken either as a remedy for or as a preventive against, malaria. The ship s doctor must also pay attention to the possibility of vaccinia generalized or not, and to the skin reactions after immunization against

plague, yellow fever enteric fever, paratyphoid A & B fever or cholera.

The ship's surgeon must be aware of the fact that with the crew skin diseases may be caused through contact with the cargo These skin affections may give rise to diagnostic difficulties if they resemble in some way tropical skin diseases



1084 Ringworm due to Trichophyton rubrum.

*(Simons–Amsterdam)*

When we look back at this long but certainly incomplete list of skin diseases which a ship's doctor may meet with on his voyages it is obvious that his work in the dermatological field is not so simple He must think of everything His task is not finished, however with diagnosing the disease and treating the patient according to his ability and judgement The ship's surgeon is not only the medical attendant on board, he is also the officer of health watching over the health of

all on board. He must take measures to prevent the spreading of contagious diseases, in this case of communicable skin diseases. These measures must be taken inconspicuously, as it were noiselessly, so that no panic is caused on board. This part of the ship's doctor's task demands special tact and great knowledge of human character, for he must obtain the voluntary cooperation of the patients without in any way offending them.

The most drastic measure which can be taken on board is the



1065. But this "ringworm" proved to be cutaneous leishmaniasis recidivans. *(Sagher-Jerusalem)*

complete isolation of the patient. The ship's doctor must adopt this course only when it is absolutely necessary. If, however, he considers isolation unavoidable, it is preferable to admit the patient to the ship's hospital to be treated there. Isolation in a cabin is never perfect. It may be desirable to forbid a patient to attend the general meals or use the common bathtubs, swimming pool or shower baths. In a case like this the ship's doctor should see to it that the patient is served in his or her cabin and a bath or shower is assigned to him, e.g. the bath of the

ship s hospital. That all this must be done with the necessary delicacy needs no further explanation nor that care should be taken that the patient is always given the same dinner service

The ship s doctor should never forget when treating contagious skin diseases to look for contact infections In the first place among those who share the patient s cabin, but also among those of whom it may be expected that they have been infected. With the members of the crew this examination is rather easy with passengers a good deal of tact is required as the examination must be done inconspicuously The consulting hour mostly offers plenty of opportunities for this purpose for a visit to the doctor during his consulting hours is considered a kind of diversion on board and most passengers go there once or oftener

In case of scabies or vermin the ship s doctor of course takes the necessary measures for disinfection. Especially when there are patients with athlete s foot on board, he must not forget to disinfect the wooden floor slats and the mats in the bathrooms and showers by having them scrubbed daily with boiling water in which bleaching powder has been dissolved After this they are washed with clean water to remove the chlorine The lavatory seats are cleaned with a solution of formaldehyde and then washed with hot water The ship s surgeon must not forget either to have the shoes of sufferers from tinea pedis disinfected by having them stuffed with cotton wool soaked in formaldehyde solution after they have been cleaned. Twenty four hours after the cotton wool has been in the shoes it is removed and the shoes are dried. Then they can be worn again Socks and underwear can be disinfected by boiling them they must be changed every day

When cooks and stewards and other personnel who handle food, suffer from a contagious skin disease they must temporarily do other work which does not bring them into contact with food. This also holds good if they are suffering from a venereal disease in a contagious stage Stewards are excluded from table-service" when they are suffering from a skin disease which is conspicuous and thus repulsive" to passengers

Finally the ship s doctor should see to it that neither the ship nor the cargo nor the passengers will experience any delay or trouble

from the port authorities The best way of attaining this is to take all possible measures to prevent the spreading of infectious skin diseases.

### SKIN DISEASES AND QUARANTINE

Practically speaking there are no sharply defined quarantine regulations for infectious skin diseases Under the Immigration Act of 1924 all those suffering from a loathsome or dangerous contagious disease" are excluded from admission into the United States. The definition is rather vague and its interpretation is left entirely to the port doctors supervising disembarkation. Most South American States have identical regulations

With respect to leprosy patients the regulations in most countries are in general very rigorous concerning admission, since modern views about the contagiousness of this disease are not yet common knowledge to the authorities

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# ADDENDA

INCLUDING PASSAGES ON
PSYCHOSOMATIC DERMATOLOGY
URBAN AND RURAL INFLUENCES, ETC.

AND

# EPILOGUE

# ADDENDA (Alphabetical)

Bejel. CRONCKA, (the Med. Illustr (1952, 6-8 401) contributed a paper from which we would quote the following "No cardiovascular or neurological lesions were found, although minor degrees of both forms have been described by AKWARI (Brit. J Ven Dis., 1949 25). It has been suggested by AKWARI that common drinking vessels may spread bejel, thus explaining the initial lesion at the mouth" Proof of bejel not being only mild disease has been given by JONES in his article on mutilating bejel in the Brit. Journal of Venereal Diseases of 1953 29-2.

Cancer of the skin is relatively rare among Indians (KHANOLKAR in Acta Un. Intern. contra Cancrum 1950 6-881). The incidence in Indians is 1 4 per cent of all cancers while amongst Non-Indians it is 18 5 per cent. This difference may be due to the pigment-factor Out of 436 cases of skin cancer in Bombay (SIRSAT



1086–1087 Sulphone-cure of leprosy (note saddle nose.).

*(Simons–Amsterdam)*

Indian J Med Science 1952 6-11) 250 were squamous cell carcinoma, 152 basal cell carcinoma, 13 carcinomas of the sweat and sebaceous glands and 20 malignant melanoblastoma. Fo of the latter were found in Europeans. This incidence runs parallel with higher incidence of skin cancers in Non-Indians. SHAPIRO KEEN, COHEN and MURRAY in Johannesburg found skin cancer relatively rare in the pigmented African Among 50 cases there were 12 albinos. In these authors experience mal gnant melanoblastomas are as frequent in the South African Bantu as in the European and more frequent than in the American Negro. In the South African Bantu malignant melanoblastoma runs a less virulent course, and tends to remain localized to the regional lymphatic system. (Brit. J Cancer 7 1953 45–57).



1090 Psoriasis in the Negro.
*(Orw G Casta-Belo Horizonte)*

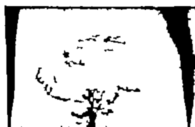


1091 Vitiligo in the Negro
*(Orw G Casta Belo Horizonte)*

perseverance in the use of drugs for it might be, several years – and even years of treatment might end in disappointment and failure — this disease can today be cured within a year The illustrations which were made between the publication of Vol. I and Vol II are very clear examples showing the success of the therapia sterilisans magna by sulphones. Of the many communications published about leprosy since the appearance of Vol. I we will here mention only a few

TENDRUM wrote in considerable detail about "The name Leprosy" in the American Journal of Tropical Medicine 1952 1–6.

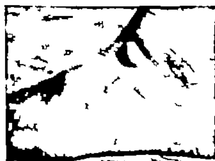
DUBOIS, in the Bulletin des Séances, Bruxelles (1952) 13–1 had an interesting



1092. Late bejel at a common site.
*(Cronche–London)*



1093 Consecutive depigmentation in bejel.
*(Cronche–London)*



1094 Juxta-articular nodes in bejel.
*(Cronche–London)*



1095 Early bejel.
*(Cronche–London)*

contribution concerning inoculations of leprosy He concluded that the disease should be considered inoculable be it only very rarely

FLOCH stated in the Bulletin Soc. Pathol. Exotique of 1953 45–3 that the negative lepromin test may become positive by the sulphone therapy

With regard to therapy reference may be made to LOWE (Brit. Med. J., 1952 746), who recommends ACTH or cortisone in case of complications in sulphone therapy For leprosy itself he advises against ACTH or cortisone, because the necessary tissue reaction is reduced, thus alleviating symptoms during therapy

but aggravating the underlying disease which is held in check by the tissue reaction. This opinion is shared by SAMPAIO, DE SOUZA-LIMA, NAHAS, and others.

SCHUJMAN (Int. J. of Leprosy 1952, 20, 1, 31–8) reports favourable results from the aldehyde derivatives of thiosemicarbazone in all forms of leprosy. The therapy was well tolerated.

A good survey of the treatment of leprosy was given by COCHRANE (Brit. Med. J. 1952 (Dec. 6)) and another by LAVIRON and COTTET in the Presse médicale 1952, 60–39.

FLOCH (Bull. Acad. Nat. Méd., Paris 1952, 14–15) found that the necessary sulphonaemia of about 1 mg per cent. remained constant when the patient took

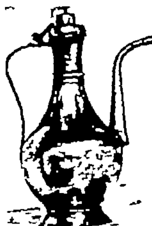


1096. To the artefacts, including those which are produced for religious purposes, belongs also this "saucer-lip" of the East Sudan women. This propably does not originate from primitive "make up" but on the contrary from a "make down" since it was introduced by the men in order to disfigure their wives and repulse Arabian woman hunters. Later this deformity became high fashion. A similar condition is known among Bahia women (Brazil). See also Fig. 620 (page 900). Most interestingly there is no evidence of infection nor of keloid formation of the lips (See the ears).

600 mg D.D.S. orally twice a week, or 800 mg once a week. He adds 5 mg belladonna, and 200 mg calcium carbonate to each tablet of 100 mg. D.D.S. and is also in favour of simultaneous treatment with vitamin $B_1$ complex. LATAPI, BARBA, RUBIO, ROCHA GUZMAN and CASTRO ESTRADA treated 14 patients (13 being of the L-type) successfully with *isoniazid* during 7 to 9 months. (3 to 5 milligrams per kilogram bodyweight daily, no toxic manifestations) (J. Invest. Derm. 1953, 21, 1). Contrary to the major tuberculoid leprosy mention should be made of the *minor tuberculoid form* with only one or few small macules, which spontaneously regress except for the analgesia. For the knowledge of this mild form credit should be given to the work of C. L. S. DOULL and RODRIGUEZ in the Philippines (Int. J. of Leprosy 1942, 1948 and 1949.

Kochard and Saoher (Journ. Invest. Derm. 1953, 21-2?) found that the specificity of the tuberculin reaction is not influenced by lepromatous leprosy.

**Lichen simplex chronicus in Orientals.** After Rein and Snider had drawn attention to the high incidence of lichen simplex chronicus in Orientals (Arch. Derm. & Syph. 1952, 66-612), Kochard (Australia), who had worked many years in Shanghai, reported the high incidence of this condition, localised in the neck, in the native population. He regards this dermatosis as most probably due to contact dermatitis from the clothing (Shanghai dress). In this respect



1097 A Turkish "ibrik" for washing ("taharet") the anus after defaecation. This is customary in the Near and Far East. It is said that anal pruritus, for this reason, is less frequent in the tropics. In Africa and South America this habit is uncommon, but in these regions regular bathing includes anus-washing.
(See footnote on the next page)

*(Simons—Amsterdam)*

Kochard referred to Grant Peterkin's khaki drill shirt dermatitis (Arch. Derm. & Syph. 1953, 67, 5 and 1948, 58-249 respectively).

**Lymphopathia venerea.** Pirila, Helsinki, described intra- and extra-cellular granules in pus from 18 cases of lymphopathia venerea, which he considered to be, most probably, causal (Dermatologica 1953, 106-1)).

**Maduromycosis.** Mackinnon (Ann. Facul. de Med. Montevideo 1951, 36-4) published a detailed study of a number of fungi isolated from the *white grain* type of mycetoma. Monosporium apiospermum should not be regarded an imperfect form of Allescheria boydii, and the Acremoniella lutea and Pseudoallescheria sheari are identical with Monosporium apiospermum. Cephalosporium recifei Area Leao and Lobo and C. falciforme Carrion were the most important of the strains of Cephalosporium. The so-called C. granulomatis Weidman and Kligman (similar to C. acremonium) are probably contaminants. Four strains of fungi from the *black grain* mycetoma occurring in the Sudan and Somaliland were compared

with Madurella ikedae Gammel and Madurella americana Gammel and M. mycetomi. All were found to be identical, but different from M grisea Mackinnon a black grain type from South America.

According to AJELLO (Americ. J Trop Med. and Hyg. 1952 1-2) Allescheria boydii is an important cause of mycetoma. It is found chiefly in its imperfect form Monosporium apiospermum. The fungus could be isolated from soil by inoculation into mice but not by means of direct cultures

Pregnenolone acetate produced an apparent cure in a case of Nocardiotic mycetoma in a child (200 or 300 mg daily for eight months – no evidences of toxicity). (LAMB, KELLY SHACKLEFORD REBELL and KOONS – Arch. Dermat. and Syph. 1953 67 2).

**Measles.** *Serampoor or tropical measles* which had not been mentioned in Volume I should receive attention, because of the devastating effects and high mortality This has been the case in a notorious epidemic in the Fiji-Islands in 1874 when 25000 patients died, and among the children of Internees in the Far East after the second World War Actually there is no difference between measles and its tropical "form" Opposite to an incipient type ("*rougeole en miniature*") in which we found but Koplik s spots, the children not being ill, the disease – without sulphonamides may turn into a serious stage, with bronchopneumonia, otitis and even noma. The macular eruption may become haemorrhagic.

**Milker's nodules,** probably due to paravaccinia, were found by KATZENELLENBOGEN in the Judean hills (Dermatologica 1952 105-2)

**Mycology** VANBREUSEGHEM (Bull. l'Acad. Roy de Méd. 1953 6-18/1) has published a contribution to tropical mycology stating that 68 per cent. of cases of tinea in the Belgian Congo are caused by Microsporons, and 32 per cent. by Trichophytons. Epidermophyton was found in only 0.3 per cent. of the cases. From geographical point of view there are, (a) the "cosmopolitan" fungi, i.e. T violaceum, T rubrum, and E. floccosum (b) the African and Asiatic fungi, T ferrugineum, and T (or Langeroni) soudanensis, and (c) two dermatophytes which ha e not yet been described outside the Congo, but may at any time leave the country i.e. M. langeronii and M. rivalieri. T violaceum and its depigmented form, T glabrum are found exclusively in the mountainous districts. Most interestingly M audouini, and M. canis could not be found in any of the 500 patients examined. It is, so far unknown why M. audouini should be incapable of crossing "la barrière méditerranéenne" and T schoenleini, although frequent in North Africa, can hardly be found in the central parts of this Continent. VANBREUSEGHEM suggests that the influence of the sun is a factor in the epidemiology of certain fungi Futhermore 9 cases of chromomycosis were found, most of which had initially been taken for yaws. Pityriasis of the face and even of the scalp is said to be quite common in the Congo. (N b. pityriasiform framboesides?)

**Nodular vasculitis.** Two cases associated with hypertension were reported in Negro women by IRGANG (Arch. Derm. and Syph. 1953 67 2). Diagnosis cannot be made without histologic study

**Pigmentation.** Demarcation lines of pigmentation on the inner sides of the extremities have been described by M UTAMA and MIURA in Japan. (Osaka Med. J 1942 13 9 and Tohoku J Exp Med 1952 56/1-2). The present writer observed the lesion on the calves of a Dutch girl born in Indonesia. The demarcation line disappeared by the age of 12 or became latent because of regular sun-bathing

Pinta. KAHN and GUTTUREZ VILLEGAS (Am. J Syph. 1952 36-5 found the same serological pattern in pinta and syphilis, and similar to, although not identical with, that produced by yaws. Some more contributions on the microscopy of pinta, which are highly interesting, have been published by EDMUNDSON ARNOLDO LOPEZ RICO and SIDNEY OLANSKY in the Americ. J of Syph. etc. 1953: 37 3.

Presbyderma This name has been given to a skin showing lichenification and keratosis by thickening (COLBOURNE, EDDINGTON and HUGHES, Bull. trop. Med 1952 49-2). In our opinion, "presbyderma" should be a good synonym for he senile skin, which, on the contrary is atrophic, freckled, and partially keratotic.

Prickly heat versus clothing dermatitis. In a personal communication GRANT PETERKIN drew the attention to clothing dermatitis due to chrome in khaki drill which he found sometimes mistaken for prickly heat by medical officers. Once the patients stop wearing the khaki dyed with chrome and use vat-dyed material they have no further complaints

Pruritus due to hetrazan is considered of pathognomonic value in onchocerciasis. It is hardly ever found in other types of filariasis (BRUCH, in Rev Colegio med. de Guatemala 1951 2-1).

Pruritus ani. As has been said in Volume I, page 117 the greater infrequency of anal itch in the tropics must be attributed to the more frequent bathing, of course coupled with anus-washing In some regions, *e g* the Orient and South East Asia, the habit prevails of washing the anus after defaecation, which further reduces the occurrence of pruritus ani. This is of particular significance in view of the statement that pruritus anl is a psychosomatic affection, supposed to originate in complexes set up in youth, *inter alia* through toilet and bowel-training, disturbances of psychosexual development, etc. But it is precisely in those countries where toilet training is part of a rite or "anal ceremonies" (paederasty in the initiation of young men [1] among Central American Tarao-Indians [2]) that pruritus anl is less frequent We have met Negro tribes who live hygienically but actually have most complicated defaecation-habits, since their faeces are tabu or may be prone to the *mana* (magic powers) of their enemies (Cf. Simson hairs). Indeed, the "black bottom" is not only important as dance!

*Pruritus and eczema scroti* are also less frequently seen in the tropics than in those countries, where people wear thick woollen underpants. The theory has been put forward that this dermatosis is psychosomatically due to conflicts in education. But it should be remembered that touching the genitals is not only unpermitted by educational ethic, but also fully tabu among some tropical peoples.

*Pruritus and eczema vulvae* are not often observed in women of some native

[1] In the Near and Far East special pitchers are kept for anus-washing (*e g.* the *tabert-ibrik* in Turkey and the *tjebok-bettik* in Indonesia), and a ritual bath is taken after coitus Washing of the feet, because they should be as clean as the face, has become common temple-ceremony

[2] This ceremony implies the introduction of the adult male s power into the initiated puber

Among these Indians "couvade" (i.e the father taking to bed, when his child is born) is also practiced, in order to mislead the demons and thus protect his wif and child.

Most remarkably oral training against the much more obstinate habit of thumb-sucking does not cause oral or circum-oral pruritus.

tribes. In our opinion this is chiefly due to the fact, that they do not wear heavy knickers or sanitary towels and that, whenever they do wear those garments they are fortunately not in a position to wash these in water containing soda or chlorine. The present writer found, that in Holland, out of 50 women, suffering from eczema vulvae, 46 were of the lower classes, apart from the climacterium and 43 having used thick sanitary towels usually made of swanskin flannel, which are washed in a soda solution and bleached afterwards in chlorine. Of course one does not state that pruritus vulvae is principally due to sanitary towels, but external factors should receive great attention.

**Psychosomatic and somatopsychic dermatoses.** Since psychosomatic dermatoses are regarded as (a.) the cutaneous manifestation of a repressed psychogenic conflict, (b.) a mere (but true) provocation of an already existing, though perhaps latent, skin disease by emotional factors or (c.) as those dermatoses, which develop in a certain type of character (personality structure), having perhaps been provoked by an emotional crisis, this branch of dermatology is still open to dispute. In many cases the psychological *effect* of a condition is retrospectively regarded as primary: the patient considering his induratio penis for example to be due to onanism in youth etc. Psyche and skin do certainly influence each other: one has only to determine in which direction the spiral turns, according to which distinction should be made between psycho-somatic and somato-psychic. The personality structure may also be explained backwards, for that a certain patient is anxious in his approach to his surroundings (and therefore works hard) since he does not want to be shown up, is self-evident. It has been stated, that people with infestations are of low intellect, but may not the reverse hold good, since people with a low intellect are often unhygienic? In our p.o.w. camps animal parasites did not show preference for the intellectuals. Moreover a low intellect is not identical with an emotional crisis or psychogenic conflict. Conversion dermatoses (*stigmata*) do not constitute special skin diseases and they usually develop in the absence of any dermatosis. Hardly any stigma-disease has stood the test of critical investigation. *Artifacts* by which the skin is deliberately wounded, differ from psychosomatic dermatoses, since the latter arise spontaneously, subconsciously and after a (long) "incubation period". Closely related to the artifacts is tattoo. The soldier and sailor decorate their bare arms by tattooing from the same motive as women pierce their earlobes and stain their nails. The choice of the design has hardly any importance, since it has been chosen according to fashion of one's milieu. Moreover most tattooing has been palmed off on the victims by professional or amateur tattooers. These few remarks obviously do not detract in any way from the bona fide part of psychosomatic medicine, which should not become a port of refuge for unsolved cases. In those dermatoses which are suspected or judged to be psychosomatic, psychiatric intervention for both diagnosis and therapy is essential. (See also page 117 to 122 and the notes on pruritus ani and urban and rural influences in these addenda).

**Resistance to infections.** It has been contended that there is less chance of infection in the tropics, although the people there so often get skin wounds, in addition to which they make tattoo holes in the ears and the nares, artificial enlarged lips, circumcision etc. In tropical p.o.w. camps, indeed—where almost

all facilities for proper disinfection were lacking — we rarely found infections, despite numerous traumas, including circumcision of the sentries, who were infatuated with this form of "tattoo" (Dermatologica 1948 96-2). These practices however are also found in non-tropical regions. Only statistical investigation can elucidate this problem.

**Scabies.** Among the cutaneous disorders met with in the Belgian Congo LAPIERRE (Bull. Acad. Méd. Belg. 1952 17-4) found scabies to be most frequent, particularly among children, the parents having become more or less desensitized since they



1098 Local prickly heat of the right shoulder due to prolonged exposure to strong electric light.

*(S[illegible] – Amsterdam)*

show but a few lesions. Scabietic lesions constitute a common portal of entry of yaws.

**Scars of the upper eyelid** has been reported by FUCHS (Urol. & Cut. Rev. 1952 55-4) among Chinese. They were always seen on the temporal part and even on the temples. It has been said that these scars originate from furunculosis, from pinching up a fold of skin with bamboo to prevent entropion and so on, but FUCHS discards these opinions and he suspects a parasitic or infectious disease, perhaps leishmaniasis to be the cause.

**Schistosome dermatitis.** CORT (Am. J. Hyg. 1950 52-3) states that the first penetration of Sch. japonicum does not cause any lesion, but that the dermatitis is due to super-infection. Urticaria, papules and [illegible]ches are caused more often by the non-human Schistosomata. Secondary infection may obscure the essential dermatitis. Statistical survey and animal experiments revealed that "*Kabure*" a Japanese schistosomal dermatitis is actually an allergic phenomenon. (ISHII and OGAWA in the Yokohama Med. Bull. 1952 3-2).

**Scorpions.** A most interesting article on the scorpion problem in Brazil was published by DA SILVA (Am. J. Trop. Med. and Hyg. 1952 1-3). Of over ten thousand scorpions captured, 80 % were Tityu serrulatus. Three other species were T. bahiensis, Bothriurus bonariensis and B. magelhaensis. In Ribeirao Preto north-east of Sao Paulo in Brazil 1331 persons were recorded (during 7 years) as having been stung. Eighty – all children – died. Most stingings occurred at the start of the rain breeding season. In Arizona 3000 scorpion accidents are reported annually, 60 % which end fatally (S[illegible]).

**Skin colour.** Sometimes it is taken for granted that inhabitants of tropical territories have various skin colours and that some of them (Australia) can even adapt

the colour of their skin to their surroundings in the same way as a chameleon. The name Redskin originates from the habit of painting the skin red with the juice of the Bixa orellana. The Yellow Race owes its epitheton to the pale skin of some Mongolian tribes. The majority of the Yellow Race, however is tan-coloured. In as far as the difference between black and white skins is concerned, this is of greater political than medical importance not only because many races regard themselves as chosen, but perhaps also because of the association of white with goodness and black with evil. The story that mimicry is found in humans is just as much legend as it is for the chameleon because mimicry of the human skin is actually no more than a form of camouflage, employed by the natives by painting their skin the same way as the hunter wears green clothes. (See also Vol. I page 52).

**Speculative waters.** This term may serve to cover those fanciful theories which are based on wrong observation or interpretation, or unfounded conclusions. We already touched upon this in relation to tinea albigena, the prodromata of leprosy and the so-called epidemic occurrence of leprosy in mediaeval Europe, when almost any skin disease was called "lepra" (even measles have been termed lepra minor"), etc. Then there are certain fashionable terms often used speculatively *e.g.* constitutional, essential, focal infection auto-intoxication, etc. The concepts which these words represent—whose great importance the present writer is far from gainsaying—have unfortunately too often been used by way of embarrassment diagnosis, as a cloak for ignorance. For the search for the aetiology of many insufficiently understood skin diseases, investigators have often thought they had found the "philosopher's stone" by applying these terms to all, what we should like to call *X-dermatoses* (dermatoses of unknow origin). We should, however be fully aware that the X is not the same in every disease. No one will deny that the constitution into which a disease settles itself must be thoroughly examined, and treated, since without a forest there cannot be a forest fire. But the forest fire is kept at bay by fighting the fire not by cutting the trees down or making them fire proof. How often have not these speculations led to set back and failure Again, the indiscriminate application of bona fide science is another speculative exercise Thus, the fact that a patient benefits from the administration of calcium, hormones or vitamin drugs may well, in special cases, be possible or an accidental circumstance *post hoc* instead of *propter hoc* but "paratherapy" does not justify its being proclaimed science. It may only lead to Therapeutic panic, implying the complete senseless, desperate application or consumption of different medicines without waiting for results, *i.e.* without giving them chance This has been dealt with in Volume I page 148.

**Terminology** Since the jungle of dermatological terminology is not only tropical, but embraces also non-tropical terms, a list of common terms has been included in this book. The drafting and completion of this list involved work covering a number of years and opinions, in some cases, were so divergent that we had to distil our conclusion from them.

**Urban and rural influences.** The opinion has sometimes been expressed that eczemas are less frequent in the tropics, because there are fewer psychic inhibitions in small communities But superstition, magic rites, suppression of erotic feelings because of traditions complicated matrimonial ceremonies, etc. may on the contrary constitute serious psychic traumata precisely in small communities with their closely knit social forms and exchange of gossip. It can perhaps be admitted that in the woods and countryside young children can play more freely and are less

subjected to coddling and to enervating influences of big cities, traffic, etc., but on the other hand Nature, in which every tree and every water represent a divine or evil spirit, parental superstition, and the children's cohabitation with their parents are, in their turn, possible reasons why the emotions of even young children living very early in fear of demons may be stirred in the free atmosphere of Nature. Those who have lived in the tropics will agree that, prior to a conclusion that psychosomatic factors do not prevail various other factors (sun-exposure, clothes, bathing, diet, less contact with "Western chemicals" etc.) should be excluded. Not long ago it was generally accepted that tuberculosis and caries were uncommon among natives and that tropical individuals were resistant to malaria, progressive paralysis, trichophytia and so on! (See also pruritus ani and lichen simplex chronicus).

**Weber Christian disease.** SAMITZ and COLETTI described a case in Negress (Arch. Derm. and Syph. 1952 65-4). This is the second case published the first being that of JOHNSON and PLICK (Arch Pathol. 1949 48).

**Yaws.** BARNARD had a very interesting paper in the Journal of Trop Med. and Hygiene (1952, 5-6 100) bout yaws, stating that " various species of flies can, and do, act as mechanical vectors of yaws but the extent to which this is an important or even common mode of dissemination is uncertain, and probably varies in different localities" In the Western hemisphere *Hippelates flavipes* In India and Malay *Siphunculina funicola*, and in Africa, Asia, and Australia generally the house fly or other species of *Musca* (see Vol. I page 13). Some important contributions concerning the campaign against yaws have been published in the *Bulletin* of the World Health Organization of 1953 8/1-2-3.) by HACKETT on his experiences in Africa ("Consolidation phase of yaws control"), by LEVITAN, RODRIGUEZ, JACOBS, PETRUS and DURAND on treatment of infectious yaws with one injection of penicillin, 600,000 Units being regarded adequate for mass treatment, by HILL on antibiotics other than penicillin, stating that, were it possible to produce aureomycin, chloramphenicol, and terramycin in repository form, as has been done for penicillin, their claims to be used in treating yaws would be much stronger Furthermore by REIN on diagnostic aids in mass-treatment campaigns against yaws, concluding that in areas of high prevalence it may be feasible to treat the entire population without serological examination and by SOETORO and WAERTO on their experiences with yaws control in Indonesia.

[1] Here one may only think of *animism i.e.* the belief that all Nature is endowed with deity *manism* e. the belief in secret powers (everybody and everything with *mana* should also be regarded *tabu i.e.* sacred and dangerous), *fetichism Moloch-culture* with its human sacrifices, *cannibalism obligatory suicide* and *infanticide* *manifold initiations* (see also pruritus ani) and *purification rites Lama-istic celibacy* (one should read their prayer's scroll!), strong fixation to genital and sexual culture with *circumcision tatooing* *p of the prepuce* (Indian tribes from the Amazone area), *artificial hypospady* (some Australian tribes) and its equivalent *artificial finger mutilation* in the female (East Coast Australia) *koro* or *shook yang* (South East Asia – see Vol. I page 51), *guna guna* (see Vol I page 34 and 120 and Fig 128) and the so intensively emanating *totemism* by which the slightest love-making will seriously be punished and by which children may e en not face their mother or father

In this connection attention should be paid to non-typical yaws-lesions, *viz.* psoriasiform- pityriasiform- and perlèche-form framboesides!

**Miscellaneous.** From a large number of photographs received we can find space for reproduction of the following only: one of vitiligo, one of psoriasis and one of localized prickly heat caused by prolonged exposure to electric light.

R. D. G. PH. SIMONS.

# EPILOGUE

## In the Jungle of Dermatology

R. D. G. Ph. SIMONS
Amsterdam

*To Helen from P O W No 5686*

In the attempt at exploring the "jungle of dermatology (Vol. I Chapter I) we have had occasion to observe how many terminological and other lianas entangled and obstructed our path. This scientific jungle thrives on misconceptions which remain behind, rotting and fertilizing the soil and affording nourishment for deeply rooted opinions, which are merely obstructing weeds. Some of these weeds even grow into idolized forest giants. Woe to him who has the presumption to hack them down!

Only bona fide, not intuitive "hearsay" science, as SPINOZA has called it, can help us to cut a path, if we are not to wander vaguely baffled, through a maze of medical superstition. Many so-called established facts will have to be transplanted, having first been subjected to a scientific selection. The "rebuilt science of textbooks, in which authors merely repeat what others have written, and thus create tradition, should be replaced by team-work. We have to guard against "quandary diagnoses, in which the label of some fashionable diagnosis is tagged on to an affection whose origin is obscure, and we should beware of fishing in speculative waters

*Wishful thinking must make room for logical thought*
*Logic must follow objective observation and*
*Conclusions should be based on experiment*

*The solution of our problems does not principally lie in the exchange of opinions but in investigation*

It is not only in the tropical night of medical science that the many commercial Scheherezades whisper their 1001 Arabian night fictions in our ears – those promising temporarily fascinating assurances of success – for the following night there comes a different story after which the first charmer gently retires into the nocturnal dusk, the physician having meanwhile been hushed to sleep. Such promises act like sedatives on our intellect and professional conscience, and we end by observing in one's dreams successes which in actual fact are nothing of the kind.

Only slowly does genuine science penetrate deeper and deeper into the jungle in response to the call of the drums and the agonized cries for help from the suffering natives, tormented by helminths, hexapoda, acarina, treponemata, bacteria, invisible viruses, fungi etc., and *calling for that medicine man whose magic is science*. For this alone will put the tormentors to flight.

# INDEX*

*Main references are indicated by page numbers in heavy type*



* I am greatly indebted to Dr J J J for the compilation of this Index.